THE GEORGE BLUMER

EDITION OF

BILLINGS-FORCHHEIMER'S

THERAPEUSIS OF INTERNAL DISEASES

SUPPLEMENT

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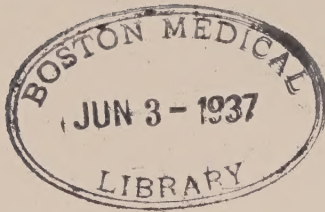### CARE AND MANAGEMENT OF MALADIES
AND AILMENTS OTHER THAN SURGICAL

SUPPLEMENT

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EDITED BY

GEORGE BLUMER, M.A. (YALE), M.D.

DAVID P. SMITH CLINICAL PROFESSOR OF MEDICINE, YALE UNIVERSITY SCHOOL OF MEDICINE,
ATTENDING PHYSICIAN TO THE NEW HAVEN HOSPITAL

PREFACE

A REMARKABLE tribute has resulted from the request of Dr. Blumer to the contributors to his Edition of the Billings-Forchheimer Therapeusis for supplementary material and corroborative data. In very few instances have original authors found occasion to emendate or modify their articles written in 1924. The space then allotted to Dr. Blumer was limited to six volumes, necessitating the inclusion of only such text as passed his rigid censorship regarding facts that were ready to withstand the keenest scrutiny.

Categorically, there are subjects now sufficiently matured to be associated with this select company, which four years ago were unripe; others that reflect the vast strides made in preventive therapy, a field that is destined to characterize this age of medicine, even as "therapeutic nihilism" describes the latter years of the nineteenth and the early years of this century; still others that present the recent advances made in radiotherapy, both Roentgen and radium, as applied to malignant processes and sanguinopoietic disturbances.

The original division into volumes of necessity took into consideration an equality of size, and yet, as with any well conceived work, it proved to be logical. Some divisions have been supplemented more extensively than others, but with a few exceptions the broad outline remains the same. On the following pages of this volume the reader will find a list of contributors and a complete table of contents in conventional form, but à propos of the general plan he is referred to the prefaces of each volume for the Editor's comments on chapters that are particularly significant.

In some instances it is advisable to read original text in connection with a supplementary article. For example, the Stokes article on recent advances in the treatment of syphilis, while complete in itself, is distinctly supplementary. An additional reason for its mention here is the fact that it illustrates a type of advance, as does the chapter by White on the use of quinidin in disorders of the heart beat.

CONTRIBUTORS TO SUPPLEMENT

HAROLD L. AMOSS, M.D.

Associate Professor of Medicine, Johns Hopkins University School of Medicine

Serum Treatment of Erysipelas

JAMES B. AYER, M.D.

Professor of Neurology, Harvard University Medical School, Boston; James J. Putnam Clinic, Boston

The Therapeutic Value of Lumbar Puncture and Other Methods of Approach to the Cerebrospinal Fluid Spaces

ALVAN L. BARACH, M.D.

Member of the Department of Medicine, Columbia University, Physicians and Surgeons College; Assistant Physician to Presbyterian Hospital, New York City

The Therapeutic Use of Oxygen in Pneumonia

C. S. BECK, M.D.

Associate Surgeon to Lakeside Hospital, Cleveland; Assistant Professor of Surgery, Western Reserve University, School of Medicine, Cleveland

The Surgical Treatment of Diseases of the Heart and Pericardium

A. E. BENNETT, B.Sc., M.D.

Instructor in Neuropsychiatry, University of Nebraska, College of Medicine, Omaha

Non-Specific Protein Therapy of Multiple Sclerosis

KENNETH D. BLACKFAN, M.D.

Professor of Pediatrics, Harvard Medical College and Director-in-Charge of the Infants and Children's Hospital in Boston

Treatment of Acidosis and Alkalosis

FRANCIS G. BLAKE, A.B., M.A., M.D.

John Slade Ely Professor of Medicine, Yale University School of Medicine; Physician-in-Chief, New Haven Hospital and Dispensary, New Haven

Scarlet Fever

LAWRASON BROWN, M.D.

Consulting Physician, Trudeau Sanatorium, Saranac Lake, New York

The Present Status of Vaccination in Tuberculosis

PHILIP KING BROWN, M.D.

Medical Director of the Southern Pacific Hospital, San Francisco

The Surgical Treatment of Angina Pectoris

HENRY ALDEN BUNKER, JR., A.B., M.D.
Formerly, Assistant Director, New York State Psychiatric Institute

The Place of Malaria in the Treatment of General Paralysis (Paresis)

C. SIDNEY BURWELL, M.D.
Professor of Medicine, Vanderbilt University Medical School, Nashville

The Therapeutic Use of Digitalis

RUSSELL L. CECIL, A.B., M.D.
Assistant Professor of Clinical Medicine, Cornell University Medical School; Assistant Visiting Physician, Bellevue Hospital, New York City

The Specific Treatment of Lobar Pneumonia

CHARLES R. CONKLIN, M.D.
Medical Director, Children's Aid Society, New York City; Consulting Physician, Five Points House of Industry, New York City

Some Problems of Convalescence

JEAN V. COOKE, A.B., M.D.
Associate Professor of Pediatrics, Washington University School of Medicine, St. Louis; Assistant Physician to the St. Louis Children's Hospital

The Serum Treatment of Measles

GEORGE R. COWGILL, Ph.D.
Assistant Professor of Physiological Chemistry, Yale University, Sterling Hall of Medicine, New Haven

Vitamins

CHARLES F. CRAIG, A.M., M.D.
Colonel, Medical Corps, United States Army, D.S.M., Washington, D. C.

The Prophylaxis and Treatment of Amebiasis

E. C. CUTLER, M.D.
Professor of Surgery, Western Reserve University School of Medicine, Cleveland

The Surgical Treatment of Diseases of the Heart and Pericardium

JOSEPH C. DOANE, M.D., F.A.C.P.
Assistant Professor of Medicine, University of Pennsylvania Post-Graduate School; Instructor in Medicine, University of Pennsylvania Undergraduate School

Poisoning from Anilin, Nicotin and Cosmetics

JAMES CHARLES FOX, M.D.
Clinical Assistant Professor of Neurology, Yale University School of Medicine; Assistant Attending Physician, New Haven Hospital and Dispensary

Subarachnoid Hemorrhage

ALFRED FRIEDLANDER, M.D.

Professor of Medicine, University of Cincinnati College of Medicine

Hypotension

JAMES L. GAMBLE, M.D.

Associate Professor of Pediatrics, Harvard University School of Medicine, Boston

Treatment of Acidosis and Alkalosis

HERBERT Z. GIFFIN, M.D.

Associate Professor of Medicine, Division of Medicine, Mayo Clinic, Rochester, Minnesota

The Treatment of Polycythemia Vera (Erythremia)

BURGESS GORDON, M.D.

Medical Director, Department for Diseases of the Chest, Jefferson Hospital, Philadelphia;
Associate in Medicine, Jefferson Medical College; Assistant Physician,
Outpatient Department, Pennsylvania Hospital

A Redistribution of the Carbohydrate Intake in the Treatment of Obesity

J. E. GORDON, M.D.

Director, Division of Communicable Diseases, Department of Health, Detroit

The Treatment of Disease Carriers

NORMAN B. GWYN, M.D.

Senior Demonstrator in Medicine, University of Toronto; Assistant Physician to the Toronto
General Hospital; Consultant in Medicine to the Reception Hospital, Toronto

Acute Massive Atelectatic Collapse of the Lungs

E. VERNON HAHN, A.B., M.D.

Instructor in Surgery, Indiana University School of Medicine; Professor of Surgery, Indiana
University School of Dentistry, Indianapolis

Drepanocytic (Sickle-Cell) Anemia

SAMUEL C. HARVEY, M.D.

William Harvey Cushing Fellow in Surgery, Yale University, New Haven

Recent Advances in the Treatment of Peripheral Vascular Disease

FRED H. HEISE, M.D.

Consulting Physician, Trudeau Sanatorium, Saranac Lake, New York

The Present Status of Vaccination in Tuberculosis

GEORGE HERRMANN, M.D.

Assistant Professor of Medicine, Tulane University School of Medicine, New Orleans

The Treatment of Adams-Stokes Convulsive Syncope of Heart-Block

JOHN A. HILLSMAN, M.D.

Assistant in Surgery, Yale University School of Medicine, New Haven

Granuloma Inguinale and Lymphogranulomatosis Inguinalis

HUBERT S. HOWE, A.M., M.D.

Associate in Neurology, Columbia University; Assistant Visiting Neurologist, Presbyterian Hospital; Assistant Professor of Neurology at the New York Post-Graduate Hospital Medical School, New York City

Treatment of Chronic Epidemic Encephalitis

CHEVALIER JACKSON, M.D., Sc.D., F.A.C.S.

Professor of Bronchoscopy and Esophagoscopy, Jefferson Medical College; Professor of Bronchoscopy and Esophagoscopy, Graduate School of Medicine, University of Pennsylvania; Lecturer on Bronchoscopy and Esophagoscopy, Woman's Medical College, Philadelphia

Diseases of the Esophagus
Bronchoscopy in the Treatment of Pulmonary Disease

LAURA A. LANE, M.D., F.A.C.S.

Todd Memorial Hospital, University of Minnesota Medical School, Minneapolis

Radiotherapy in the Treatment of Diseased Tonsils

DAVID MARINE, A.M., M.D.

Director of Laboratories, Assistant Professor of Pathology, Columbia University, Physicians and Surgeons College; Attending Physician, Montefiore Home and Hospital for Chronic Diseases

Iodin in the Treatment of Thyroid Diseases

H. M. MARVIN, M.D.

Assistant Professor of Medicine, Yale University School of Medicine, New Haven; Attending Physician, New Haven Hospital

The Treatment of Heart Disease, Particularly Heart Failure, by Measures Other than Digitalis

JOSEPH L. MILLER, B.S., M.D.

Clinical Professor of Medicine, Rush Medical College; Attending Medical Staff, Cook County and St. Luke's Hospital, Chicago

Non-Specific Therapy

GEORGE R. MINOT, A.B., M.D., D.Sc. (Hon.)

Professor of Medicine, Harvard University School of Medicine, Director of the Thorndike Memorial Laboratory; Visiting Physician and Chief of the Fourth Medical Service, Boston City Hospital

Treatment of Pernicious Anemia
Treatment of Anemia, Other than Pernicious Anemia, with Diet

THEODORE F. MOÏSE, M.D.

Associate Professor of Surgery, Yale University School of Medicine, New Haven; Attending Physician, New Haven Hospital

The Treatment of Thrombocytopenic Purpura Hæmorrhagica

REUBEN OTTENBERG, A.M., M.D.

Attending Physician, Lenox Hill Hospital, Adjunct Physician, Mt. Sinai Hospital, New York City

Blood Transfusion in Septic Diseases

ASHLEY W. OUGHTERSON, M.D.
William Harvey Cushing Fellow in Surgery, Yale University, New Haven

Recent Advances in the Treatment of Peripheral Vascular Disease

WILLIAM H. PARK, A.B., M.D., LL.D.
Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College;
Attending Bacteriologist to the Willard Parker Hospital; Director of Bureau
of Laboratories, Department of Health, New York City

The Substitution of Toxoid or of Antitoxin Made in the Goat or Sheep for Antitoxin Made in the Horse for Producing Toxin-Antitoxin

M. G. PETERMAN, Sc.B., A.M., M.D.
Professor of Pediatrics, Marquette University Medical School, Milwaukee; Director of Laboratories and Research, Milwaukee Children's Hospital

The Treatment of Epilepsy in Childhood

JOHN P. PETERS, M.D.
Associate Professor of Medicine, Yale University School of Medicine, New Haven

The Treatment of Nephritis

HARRY PLOTZ, M.D.
Pasteur Institute, Paris

Local Immunity

DOUGLAS QUICK, M.D.
Attending Surgeon, Memorial Hospital, New York City

The General Care and Management of the Cancer Patient

WILLIAM R. REDDEN, A.B., M.D.
Associate Director, Department of Health Service, Cleanliness Institute, New York City. Formerly,
National Medical Officer, American Red Cross, Washington, D. C.

Treatment of Asphyxia Due to Drowning, Electric Shock, and Carbon Monoxid

J. F. ROGERS, M.D., Dr. P.H.
Chief, Division of Physical Education and School Hygiene, Bureau of Education, Department
of the Interior; Formerly Member of the Division of Industrial Hygiene and
Sanitation of the United States Public Health Service

Radio-Active Substances

LEONARD G. ROWNTREE, M.D.
Professor of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

The Treatment of Cirrhosis of the Liver

HENRY L. K. SHAW, M.D.
Clinical Professor of Diseases of Children, Albany Medical College; Consultant in Child
Hygiene, New York State Department of Health

The Modern Technic of Vaccination

SAMUEL SILBERT, M.D.

Pathologist, Adjunct Surgeon and Assistant Neuropathologist, Mt. Sinai Hospital; Chief Surgeon,
Clinic Mt. Sinai Dispensary, New York City

The Treatment of Thrombo-Angiitis Obliterans

GEORGE H. SMITH, Ph.D.

Professor of Immunology, Yale University School of Medicine, New Haven

Bacteriophage Therapy
The Calmette-Guérin Method (B-C-G) of Vaccination Against Tuberculosis

WILLARD B. SOPER, M.D.

Associate Clinical Professor of Medicine, Yale University School of Medicine; Physician to
the William Wirt Winchester Hospital for Tuberculosis, New Haven

Collapse Therapy in Pulmonary Tuberculosis

R. R. SPENCER, M.D.

Surgeon, United States Public Health Service, Washington, D. C.

Prevention and Treatment of Rocky Mountain Spotted Fever

JOHN H. STOKES, A.B., M.D.

Professor of Dermatology and Syphilis, University of Pennsylvania School of Medicine,
Philadelphia

Treatment of Syphilis

RICHARD P. STRONG, Ph.B., M.D., Sc.D.

Professor of Tropical Medicine, Harvard University Medical School, Boston

Recent Advances in the Treatment of Leprosy

PAUL D. WHITE, A.B., M.D.

Instructor in Medicine, Harvard Medical School, Associate in Medicine and in Charge of
Cardiac Clinics, Massachusetts General Hospital

Paravertebral Alcohol Injections in the Treatment of Angina Pectoris
Treatment of Disorders of the Heart Beat

R. T. WOODYATT, M.D.

Clinical Professor in the Department of Medicine, University of Chicago; Attending Physician,
Presbyterian Hospital, Chicago; Director Otho S. A. Sprague Memorial Institute
Laboratory for Clinical Research, Chicago

The Present Status of Insulin Therapy

G. ALEXANDER YOUNG, M.D.

Professor of Neuropsychiatry, University of Nebraska College of Medicine, Omaha

Non-Specific Protein Therapy of Multiple Sclerosis

H. M. ZIMMERMAN, M.D.

Instructor in Pathology, Yale University School of Medicine, New Haven

Granuloma Inguinale and Lymphogranulomatosis Inguinalis

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SUPPLEMENT

CHAPTER I

SOME PROBLEMS OF CONVALESCENCE

Charles R. Conklin

GENERAL CONSIDERATIONS

Convalescence.—The state of progressive restoration to health and strength after the cessation of disease, also the period of such restoration.

Convalescent.—One who is regaining health after sickness.

With these brief words, the dictionary disposes of our subject. In much the same brief fashion, the medical profession has been all too frequently considering it. Some part of this attitude has been due, no doubt, to the increasing use of the hospitals by the general public, for even though the patient has been referred to the hospital by his own physician, there is a distinct break on discharge, after which the patient is frequently left to his own resources; and many patients enter the hospital without having passed through the hands of any outside physician. Patients cared for all through their illness by their own physician, either in the hospital, or in their own home, also tend to slip away when the convalescent stage is reached. This is due in some cases, no doubt, to a desire to economize, but also in other cases to the fact that the tendency to specialization and pressure of modern life is leading the physician to lose interest after the acute stage is past.

This lack of proper consideration of the convalescent stage of disease and of proper provision for the care of convalescents tends to bring about the following results:

As Regards the Hospital.—The failure to achieve the full measure of benefit from its efforts. The tendency on the part of the patient to relapse and return for further treatment, or if he is held to prevent this, the increased cost per patient and the withholding of beds from other patients needing hospital care.

As Regards the Patient.—The depression and discouragement due to delayed recovery. If the head of a family, the loss of income and tendency to return to work before he is in condition to do so, in order to reduce expense and once more produce income for the maintenance of the family. Few women are willing to rest a sufficient length of time, knowing that

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the home and family are being neglected and every day added to convalescence adds also to this neglect. If convalescence is unduly delayed, there is the tendency to chronic illness furnishing a fat field for the quack and charlatan and possible permanent invalidism.

As Regards the Community.—The loss of service of a member, the increased cost for his care in the hospital, which must be borne by the community, and the possible expense for his permanent care in an institution.

During the past quarter of a century, there has been in America an increasing realization of the importance of this subject and an endeavor to meet the situation in various ways. What these methods are and some suggestions for future work will be discussed under the following heads: (*a*) Convalescent care in the home; (*b*) convalescent care in the hospital; (*c*) convalescent care in the Intramural Convalescent Home; (*d*) convalescent care in boarding or foster Home; (*e*) convalescent care in the Country Convalescent Home.

CONVALESCENT CARE IN THE HOME

In spite of all its defects, it is likely that the greater part of those recovering from disease will continue to convalesce at home. Not only those recovering from minor ailments, but also those convalescing from more serious ones, usually prefer the home surroundings. If the period of acute illness has been spent at home under the care of a private physician, the convalescence will also be under his supervision. In this case, we must hope for a greater realization of the importance of this stage of disease on the part of the general practitioner and the public, and more attention to the subject by the medical schools and other institutions.

Where the patient can afford a trained attendant, the physician has a great advantage, but in many families this is impossible, even though a nurse may have been employed during the acute stage. It is here that the Visiting Nurse Associations and similar organizations will have another opportunity to demonstrate their value. So far, most of their work, like that of the physician, has been confined to the acute stage and they have retired from the case as soon as it was passed. As their work spreads and becomes better established, they will naturally tend to develop a follow-up, which will continue with the patient until he is restored to normal health.

If the patient was referred to a hospital by his physician at the beginning of or during his illness, and convalesces at home, he should of course be under the care of the physician, but with many cases the referring to or placing of the patient in the hospital by a physician ends his connection with the case and little or no effort is made by the hospital to communicate with him on discharge. This is a matter that deserves more consideration than has been the rule in the past.

If the patient has been cared for entirely by the hospital and has no family physician under whose charge he can be placed on discharge, he will, of course, be turned over to the Out-patient Department. With these patients, a very satisfactory follow-up is being established by many hospitals through their Social Service Bureaus, whose workers not only place many in Convalescent Homes but check up those who convalesce at home and do not report regularly to the clinic.

In addition to the patients who prefer to remain at home and the mothers who cannot be spared from their families, even though ill, there are various classes of patients who are not acceptable to the Convalescent Homes. Of these, more will be said later.

It is also generally agreed that infants and little children up to eighteen months should not be cared for in institutions. The Infant Health Stations and similar methods of supervision maintained in many cities are developing a follow-up on these infants which is proving very helpful.

A large part of the population of Homes for convalescent children is made up of cases listed under the head of Malnutrition, and it is a serious question whether most of them are legitimate subjects for such attention. During June, the application lists of these Homes increase out of all proportion, although no situation calling for such a state of affairs is revealed by the Board of Health or other reports. An investigation of the application usually reveals the most trivial condition and justifies the suspicion that it is due to a desire for a vacation which shall be longer and under more favorable conditions than can be obtained at most vacation homes and camps. While this is exceptional and seasonal, it reveals an attitude of mind which is carried all through the year by some social workers. Temporary care cases, due to distress, illness of parents and other causes, are constantly referred to the Homes as malnutrition, anemia, etc., thus reducing the number of beds available for legitimate convalescents. It is to be hoped that as convalescent work develops, a better understanding of the purpose of the Convalescent Home will be established.

As regards the real cases of malnutrition, of which there are plenty, the placement in Convalescent Homes seems in many cases the only solution, but even these can be much reduced in number. In 1919, there was started in New York City, by the Children's Aid Society, a malnutrition demonstration that is still being carried on. It has been conducted under the most unfavorable circumstances, in a group of schools maintained by the Society, in the worst sections of the city, the average number of children under supervision ranging from four to five thousand. The parents are poor, ignorant and frequently indifferent. A large part cannot speak English, and this is also true of part of the children. Removals are frequent, and as the schools accommodate only the lower grades, groups are constantly being promoted to other schools, where the contact is lost. The results, however, have been most remarkable. When the work was started,

the malnutrition in some cases ran as high as 67 per cent, but in a comparatively short time it was reduced from one-half to two-thirds. Each fall it has risen, due to the admission of new classes, but it soon falls, and the general average has steadily decreased.

In the beginning all children were given a thorough physical examination and all defects recorded. A nurse then had a consultation with the parents, and after calling attention to the defects and explaining their influence on the child's health, urged them to have the defects remedied. Through ignorance, indifference or lack of opportunity, the number of parents who complied was small, but as time went on, the number who consented to having the work done by the Society was encouragingly large. With the parents' consent obtained, dental clinics were established in the schools, and dental defects, appalling in number, remedied. Contacts were made with the hospitals and tonsillectomies performed. Children were taken to clinics for further examination and treatment, and in many cases the treatment was continued by the nurse in the school, as otherwise it would have been neglected. A nourishing meal was served at noon to those suffering from malnutrition, for which a small charge was made. This not only supplied the elements lacking in the home meals, but served as a demonstration. In the middle of the morning, and in some cases again in the afternoon, milk in individual bottles and crackers were served at cost. Toothbrush drills were held and attractive posters hung about the buildings. Health talks were given and the children taught to repeat health maxims. Baths were established in some of the buildings, and the children encouraged to use them regularly. In the meantime, the nurse on her visits to the homes, through conferences with the parents, was learning about home conditions, making suggestions for their improvement, and in some cases assisting the family to obtain necessary help. When parents were indifferent, or opposed to the nurse's suggestions, they were invited to have a conference with the doctor at the school. Later the plan was adopted of having the parents of all children requiring attention call at the school at the time of the original examination, when the physician called attention to the defects and explained the benefits to be expected from having them remedied. This has resulted in a much more prompt and active coöperation, many consents being obtained before the parents leave the building. At intervals, check-up examinations are made, especially as regards the children having defects, and each fall, all the children, including the new admissions, are given another full examination. At these examinations, progress is noted and further recommendations made. When children, in spite of all efforts, fail to improve, or improve very little, they are sent to one of the Society's Homes in the country, in the hope that the change in climate and surroundings will help, and this hope is usually realized. Children, however, are not received at the Homes, until earnest effort has been made to relieve their condition

in their own homes, and the stay in the country is considered as simply an auxiliary measure. When children are simply sent to the country in the first place, the parents assume that that is the only way to treat the condition, and neither learn how, nor make any effort to remove causes, or improve home conditions. The Convalescent Homes are greatly handicapped trying to build up children with so many defects, and find them returning frequently because they have soon lost what they gained on their previous visit.

Similar work is being carried on by various Nutrition Clinics and other organizations and the success obtained proves conclusively that malnutrition can be as well and even better cared for in the patient's own home as by sending him to a Convalescent Home. Furthermore, the results are more lasting, and opportunity is given for valuable educational work. There is less interruption in the school work and, last but not least, the expense is very much less. The item of expense has an important bearing, for the number of children suffering with malnutrition in a city as large as New York is very great, and the erection and maintenance of Homes of sufficient bed capacity to care for all of them is a practical impossibility. Malnutrition work should therefore be carried on in the patient's home, and the beds in Convalescent Homes reserved for their proper work. Similar methods can readily be applied in home convalescence in other conditions and for adults as well as for children.

HOSPITAL CONVALESCENCE

A certain portion of the convalescent period must always be spent in the hospital, and the length of time varies with circumstances. Hospitals at present, however, represent so great an outlay and are so expensive to maintain, that the tendency must of necessity be to shorten the patient's stay as much as possible. Plans, therefore, for any extended form of convalescent work in the hospital itself are not likely to receive much consideration.

John Bryant in his *Convalescence, Historical and Practical,* describes at some length the convalescent work carried on in the Walter Reed General Hospital during the latter part of the war. Conditions there were, of course, exceptional, but it would seem possible that some of the work outlined could be carried on in our civil hospitals.

THE INTRAMURAL CONVALESCENT HOME

In connection with the subject of Hospital Convalescence, a valuable suggestion was made to the New York Medical Center in 1925 by its executive officer, C. C. Burlingame, in a memorandum entitled "The Medical Center Problem of Convalescence." Burlingame recommended the

erection, on the grounds of the Center, of a Convalescent Home for the care of patients from its various hospitals, to be under the same general management and supervision as the hospitals. The Center is not yet complete and the proposition, therefore, has not been taken up, but its possibilities are immediately apparent. The building would be less expensive in erection, equipment and maintenance than the hospital buildings. Because of its proximity and the fact that they will still be under the same general supervision and policy, patients can be transferred at a much earlier date than would otherwise be possible. Patients who require further treatment and, therefore, could not be sent to a Convalescent Home in the country and might not be able to go back and forth to their own homes, could still have the services of the hospital staff and the benefit of its facilities. Patients on whose recovery the hospital atmosphere was having an unfavorable influence could in some cases be transferred with probable good effect. It could act as a distributing center, and hold over, for patients going to Convalescent Homes in the country or who later were to have further operations or treatment. It would form a valuable part in the educational work of the institution.

There is a distinct advantage for a hospital to have its own Convalescent Home, either in the country or close at hand, as suggested by Burlingame. For most hospitals, however, this is impossible, and the writer has been for some time interested in the possibility of an Intramural Convalescent Home for children, that should receive patients from any and all hospitals in New York City. It would have many of the advantages mentioned above and possibly some others.

With the coming of warm weather, hospitals doing tonsillectomies are swamped, and it is often necessary to book patients two and three months ahead. As soon as cold weather sets in, however, the work falls off, and some hospitals specializing in this work often have little or nothing to do. This is due to the fear, on the part of the parents, that the child may develop pneumonia, and the fear unfortunately is justified, for the writer has seen this happen on more than one occasion. Could the child remain in the hospital for a week after the operation, the danger might be past, but this does not seem practical, and it is usually the custom to simply keep them overnight and then send them home. The kind of a home to which many return, as regards heat and other comforts, as well as the hygienic surroundings amply justifies the fear of unfortunate afterresults. Country Convalescent Homes do not as a rule like to take such cases directly from the hospital, for fear of postoperative hemorrhage, and the difficulty of returning them to the hospital in such an emergency, but a Home in the city, centrally located, could receive them and either keep them for the whole period of convalescence, which usually is not as long as for other conditions, or until they could be sent to the Country Home. If such care as this were provided, it might tend to remove the

prejudice against the winter work, and at the same time relieve the summer congestion.

Quarantine is one of the most serious problems with which all homes for children have to cope. It is not uncommon at certain seasons to have almost our entire convalescent work for children held up. At such a time, an Intramural Home, although as likely as the others to be affected, would nevertheless provide additional space for urgent convalescent cases. At times when the Country Homes were filled with children not ready for discharge the Intramural Home could act as a hold over and distributing center.

It is often necessary for children discharged from the hospital to return at frequent intervals for dressings or treatment. Convalescent Homes will not, as a rule, do more than sterile dressings, and, usually, are not so located that frequent trips can be made to the hospital. If the children are sent home, the parents, through ignorance or lack of opportunity, often fail to bring them back regularly for the treatment, and as a result convalescence is prolonged and relapses occur. If the children could be cared for in an Intramural Home, arrangements might be made through volunteer workers, or otherwise, to have them taken to the hospital regularly for their treatments.

CONVALESCENT CARE IN THE BOARDING OR FOSTER HOME

The Speedwell Society has for years carried on a very creditable work in New York City and vicinity, through the boarding of infants in private families. With infants who must be separated from the mother, it is probably the best method, although institutional care still has its advocates. This work has usually been restricted to infants and young children, but could well be extended to cover certain classes of older children as follows:

Convalescent Homes have learned by experience that it is unwise to receive children coming from contagious disease hospitals, although certified as cured, until two to three weeks after discharge, because of the tendency of such children to develop some other contagious disease as a result of cross-infection while in the hospital. These children are often in need of convalescent care which they cannot get at home. Under proper conditions, they could be cared for in Foster Homes. Children from other sources known to have been exposed to contagious disease could also be included in this group.

Children with certain contagious diseases, barring them from admittance to any Home where there are other children, could be cared for in this way.

The border line respiratory case: He is recovering from an illness, needs convalescent care, but has certain suspicious symptoms, which make the Convalescent Home unwilling to place him with other convalescents,

especially those of the respiratory type. Not being definitely a positive case, it does not seem right to place him with those who are, and he, therefore, stays at home and possibly develops the very condition from which we desire to protect him. These children could also be boarded in private homes to advantage.

Convalescent children who for any reason, mental or otherwise, do not adjust well with other children, might do well in a private family home. Normal convalescents might also be cared for in this way, in times when there is an unusual amount of illness, when the Convalescent Homes are in quarantine, or where there are no Convalescent Homes.

The principal difficulty with such a plan would be the finding of suitable Homes and the foster mother would need to be, in most cases, a graduate nurse, but thousands of normal children are cared for in Foster Homes, and children of these special types have had to be placed out in emergencies. There is, therefore, no serious reason why convalescent children should not be regularly cared for in this way.

CONVALESCENT CARE IN THE COUNTRY CONVALESCENT HOME

The greatest progress in convalescent care in the last twenty-five years has been in the establishment of Country Convalescent Homes. Where new buildings are erected, the cost of erection and equipment is much less than that of the hospitals, and private dwellings are readily adapted. The cost of maintenance is about one-half that of the hospitals, and the opportunity given for the early transfer of patients permits the handling of larger numbers in the hospitals. While the expense of convalescent supervision in the patient's own home is much less than in the Convalescent Home, the advantages of the Country Home are very great and it is generally agreed that the period of convalescence is distinctly shortened.

Although the seashore has certain advantages, an inland location for all year work and for most types of convalescents is preferred. It should be near enough to permit of easy transfer of patients, both on reception and for return to hospital in emergencies. It should be distant enough to insure quiet and a minimum of visiting by relatives and friends. In Homes for children it is well to forbid all visiting.

Where a single building is used, it is well to limit it to fifty beds. Larger Homes should consist of cottages of preferably twenty-five bed capacity. The cottage plan has the advantage that certain classes of patients can be cared for who could not otherwise be received, especially if the grounds are large enough to permit of some of the cottages being placed at a distance. It also tends to limit the ill effects of quarantine in Homes for children. There should be sufficient area of land to permit of recreational activities.

Buildings should not be more than two stories in height. For adults,

single rooms or cubicles are preferred. For children, dormitories of not more than ten or twelve beds, although twenty is permissible. Isolation rooms should be provided.

In institutions of 150 or more beds, there should be a resident physician. For those of less capacity, an attending physician is usually sufficient, except in Homes dealing with special classes of patients. The attending physician, however, should make regular visits at least once a week, as well as be on call at all times.

All Homes should have at least one registered graduate nurse. Other attendants, however, may be undergraduates.

It is well to make some provision for dental work of an emergency character, at least, either in the Home or in the vicinity.

A minimum of equipment is desirable, and the aim should be for a homelike atmosphere, as opposed to the institutional. Homes caring for special classes of convalescents will need equipment suitable for the type of case cared for.

GROUPING OF PATIENTS AS REGARDS AGE

Infants and Children Up to Three Years of Age, also Women Accompanied by Infants or Small Children.—Children, eighteen months or under, when alone, should be cared for in foster homes. When accompanied by the mother, they may be included in this group. In such cases, the mother often has also to bring one or two other small children. The maintenance, in such circumstances, of three to four beds, for the care of one convalescent infant is, however, rather expensive, though the mother, of course, acts as nurse. For this and other reasons, the number of well children should be kept as low as possible. Children from eighteen months to three years can be cared for alone. This group also includes postnatal cases as well as other convalescent women who must be accompanied by children.

Girls from Three Years to Sixteen Years and Boys from Three to Eight or Ten Years.—This is the group included in most Homes for convalescent children. The children from three to six years will need special care and the maximum age of both boys and girls will depend on the size and equipment of the home.

Boys from Ten to Sixteen Years.—Little or no provision has been made for this group. They are admittedly, a difficult problem and do not fit in either with girls, or usually with small boys. The Milbank Home for Convalescent Boys, at Valhalla, N. Y., has, however, conspicuously demonstrated that when properly handled, they can be as well cared for as any other group.

Boys from Fifteen or Sixteen to Twenty Years of Age.—This is rather an indefinite group and probably too small to justify a separate Home.

They are usually placed with men, but do not always adjust well. At the same time, they do not like to be placed with younger boys. Another difficulty is that there is seldom adequate provision for men, and as soon as there is any pressure the boys are refused on the plea that preference must be given to heads of families in order that they may return as soon as possible to their work. The best solution would seem to be to have separate provision made for them at either a Home for men, or one for boys, and with beds definitely set aside and held for them.

Adults.—Much less provision has been made for men convalescents than for women. This is partly due to the fact that there is less need for such provision, but the women and children have undoubtedly received more than their share of attention. The Adults' Home can with advantage receive both men and women of all ages. An excellent illustration of this type of Home is the Burke Foundation at White Plains, N. Y., which, under the capable administration of Frederic Brush, has become the most outstanding institution of its kind in existence at the present time. Since its opening in 1915, many thousands of men and women patients have passed through the institution, and Brush states that the mingling of the sexes under proper supervision has been of distinct benefit to them. It is to be hoped, therefore, that in future establishment of Homes, the men convalescents may receive more attention.

TYPES OF CONVALESCENT HOMES

General Convalescent Homes can receive nearly all medical cases in the convalescent stage, and surgical cases that do not require more than sterile dressings. They also do quite a little work classed as Preventive Convalescence. This, however, as regards children at least, has been carried to an extreme and should be limited to patients who have actually been under medical care. General Homes can also, under favorable circumstances, receive many patients included in the following groups, although such patients should generally be sent to special Homes.

Some Homes refuse patients convalescing from chorea, but after an experience of twenty years, the writer has failed to find any serious obstacle to their inclusion in a general Home.

Cardiac.—All general Homes receive some patients convalescing from other diseases, who have mild cardiac lesions, but cardiac patients require a special régime not possible in general Homes, and are often unhappy or hard to control, if required to observe restrictions not required of other patients.

Orthopedic.—Many patients with casts or braces or using crutches, etc., are cared for in general Homes and under favorable circumstances are occasionally permitted to return to the hospital for application of new casts or for other treatment. Orthopedic patients, however, generally re-

quire a different equipment and their convalescence is much more prolonged.

Special Diet Cases.—While most general Homes are willing, occasionally, to make slight changes in diet, if the patient is old enough and willing to coöperate, such changes in a general way are impractical and patients requiring them should be sent to special Homes.

Border Line Respiratory Cases.—These are classed with those who definitely have contagious diseases or who are suspected of having them, or who may in any way be a menace or annoyance to other patients and, therefore, should not be sent to general Homes.

Neurological.—While some of these patients have at times been cared for in general Homes, it is generally agreed that they should be cared for in separate Homes.

Colored.—Many Homes for children experience very little difficulty in handling both colored and white children in the same building, but it is seldom practical as regards adults. Special Homes must usually be provided for them. As a result very little provision has been made for colored convalescents.

Pay Patients.—In this discussion of Convalescent Homes, we are not including private sanitoriums for the fairly well to do. Aside from them, most Convalescent Homes in the past have been established on the principle that the patients could not pay and, therefore, they were not asked to contribute anything. The wisdom of this policy is now being seriously questioned. Some allowance should, of course, be made when there is sickness in the family, but most patients or their parents can contribute something and should be urged to do so, according to their means. Distinction cannot be made between patients in the Home, either according to their contribution or their standard of living, but provision should be made for patients of moderate means in separate cottages at the large Homes or in Homes especially established for them. An excellent example of the latter is the Valeria Home at Oscawana, New York.

Regimen.—There should be a definite routine planned for all patients, which should vary according to their condition. It should embrace the time for rising and retiring and for meals, rest periods, physical exercise, and social diversion. With children a moderate amount of school work is desirable. This should not be planned with the idea of keeping up with their regular school work, but as part of the routine preparing them to take up their regular duties on their return home. Advantage should be taken of the opportunity to teach regular habits of life, with attention to hygiene. A follow-up visit on a discharged convalescent child, in a home where order had not been a special virtue, found her arranging the plates, cups, knives, forks. etc., in regular order on the table, in preparation for the noon meal. Comment by the social worker brought this response from the mother: "Oh, yes, we all have to do everything just so since Mary

came back from the country." This recommendation applies to adults as well as to children. A moderate amount of occupational therapy is advisable. Patients gain much more rapidly and are more content to remain, if their time is regularly employed. Chores should be of a definite nature and not planned simply to fill time, and if they can be arranged so that the patient shall learn something which shall be of a definite benefit to him on his return home, it will be all the more helpful. A convalescent period in the country affords an unusual opportunity for nature study, especially with children. If possible, there should be some garden work.

Admission of Patients.—Country Convalescent Homes should have a city admitting office. If the expense is too great for the Home to bear, two or more Homes may join in sharing it. It is very discouraging and exhausting for the patient to make the trip to the Home and then be refused as unsuitable. A city office also saves the Home much trouble and unpleasant complications. It is a great convenience to social workers in making reservations. Physical examination at the admitting office not only determines the suitability of the patient, but gives opportunity for minor adjustments before admission.

The receiving agency should take charge of the patient at the admitting office and be responsible for his removal to the Home and return to the admitting office on discharge. Responsible adults in suitable physical condition may be permitted to return home alone, not only from the admitting office, but also, when necessary, from the Home. Children should always be held at the admitting office until called for by their parents or a social worker. This should include adolescent girls.

The method of transportation will vary according to circumstances, but the ideal plan is by automobile bus directly from the admitting office to the Home. This, however, is usually considered too expensive. Here, again, two or more Homes may share the expense.

Adult patients are usually expected to bring their own clothing, but most Homes caring for children prefer to provide clothing. In such cases, the child's own clothing is sterilized on arrival and put away until the return home.

Length of Stay.—Three to four weeks is considered a minimum stay for adults and a month to six weeks for children. The maximum can be extended up to several months, if the case calls for it and the patient continues to improve. If patients, however, do not show definite signs of improvement in three weeks to a month, it is not usually advisable to keep them longer.

Records.—Convalescent Homes should obtain from the hospital, or other referring agency, sufficient information for the patient's proper care. They should also keep a record of the patient's progress while in the Home. This should include the physical examination, the gain or loss in weight (particularly valuable with children), dates seen by the attending physi-

cian and treatment prescribed and any complications or interruptions in normal progress. Also the patient's behavior and general adjustment. The weight should be taken weekly and compared with some accepted standard. (A loss in some cases is profitable.) On discharge a report should be made to the referring agency, which should then be responsible for the follow-up.

Central Bureau.—All cities maintaining a number of Convalescent Homes should have a Central Bureau or Clearing House. This may serve as an admitting office for Country Homes having no city office and, though doing no admitting for others, may serve as an Information Bureau and keep a census, so that social workers may learn what facilities there are for the various types of cases and what vacancies are available, without calling up all the different Homes. It sometimes happens that certain well-known Homes are so flooded with applications, that they constantly have a waiting list, while others, not so well known, but doing good work, have beds to spare. Such a clearing bureau, by promoting coöperation between the various Homes, could reduce duplication and promote the development of needed lines of work. It would also compile records and develop standards.

If such a clearing bureau could be combined with a General Intramural Convalescent Home, the efficiency of both the hospitals and the convalescent Homes would be greatly increased. The primary purpose, of course, would always be to bring the referring and receiving agencies together and encourage the prompt and direct transfer of the patient, but the added facilities of the Intramural Convalescent Home, used as indicated in the section under that heading, would enable the bureau to bridge over many gaps and help in the solution of various problems.

CHAPTER II

NON-SPECIFIC THERAPY

Joseph L. Miller

GENERAL CONSIDERATIONS

History.—Non-specific therapy has been utilized, as so-called protein or shock therapy, chiefly in acute and chronic infections. More recently, non-specific desensitization has interested both the clinician and laboratory worker. Still more recently, attention has been called to a probable non-specific factor in chemotherapy. Only the use of non-specific therapy in acute and chronic infections will be presented.

The credit for the introduction of non-specific therapy belongs to Ichikawa and Kraus and Mazza. These investigators, one in Japan and the others in South America, quite independently and at practically the same time made the interesting clinical observation that typhoid fever could be modified or terminated by the intravenous injection of a non-specific vaccine. Shortly after this, Lüdke discovered that vaccines were not essential, as the same results could be obtained with an albumose. Later, Schmidt and Saxl demonstrated that milk given intramuscularly would answer the same purpose. Since then, a multitude of agents have been used, many of them proprietary, all having one point in common—the ability to cause a febrile reaction. Whether any one of these has unusual or special virtues is very improbable.

Agents Employed.—Foreign protein therapy explains many rather mysterious therapeutic results observed in the past: Rumpf's good results in typhoid, with pyocyaneous vaccine; the effect of colloidal metals in acute infections; Coley's fluid, used in the treatment of cancer, probably falls in this same group, as does Hiss and Zinsser's leukocytic extract, and Vaughan's nuclein. It also explains the sudden disappearance of fever following transfusions or intravenous normal salt injections in those patients where it excited a febrile reaction.

It is unnecessary to enumerate all the various non-specific agents that have been recommended during the past ten years. A few may be mentioned—bacterial vaccines, bacterial extracts (as tuberculin), normal blood-serum of man and various lower animals, milk, casein, gelatin, proteoses (both animal and vegetable), Witte's peptone, colloidal metals, mercurochrome, and malaria and relapsing fever inoculations in cerebral lues.

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Some of these are still considered as possessing special virtues. To those interested in protein therapy, it is more important to select one agent, and become familiar with the dosage and degree of reaction desired, than to try various agents. The writer has used a considerable number of highly lauded preparations, lured by the glowing reports of their value, but has always returned to typhoid vaccine.

Character of Reaction.—All agents employed for this purpose excite a temperature reaction. Usually we expect a chill. Dramatic results are observed only after good temperature reactions. More gradual improvement may be noted after slight reactions, as following subcutaneous or intramuscular use of vaccines. Probably, the degree of reaction bears some relation to the efficiency of the treatment. When repeated moderate or good reactions have given only temporary benefit, a larger dose with severe reactions may effect a permanent cure. This is not to be interpreted as a suggestion to give excessive doses.

The reaction in chronic infections, as chronic arthritis, following a moderate dose of typhoid vaccine (25 to 35 million), appears in one-half to one hour. There is either marked chilliness, or an actual rigor with general aching, like that observed at the onset of any acute infection. Occasionally, there may be vomiting. Not infrequently, within six to twenty-four hours, there may be a second chill. Some cultures are prone to give recurrent chills. The inconvenience experienced by the patient is not greater than occurs with the initial chill of an acute infection, and not necessarily more dangerous. There is a marked difference with which individual patients react to the same dose. In the writer's experience, it is impossible to determine just the dosage that will always give a reaction.

In acute infections, as typhoid or pneumonia, the dosage should be much smaller—the initial one not exceeding 15 million typhoid bacilli, and even then the temperature reaction may be very marked. Profuse perspiration gradually reduces the temperature to normal or subnormal. Occasionally, a degree or more of temperature may persist for one or two days.

The increase in pulse rate conforms to what occurs in fever of the same degree from other causes. There may be marked cyanosis during the chill; not more marked, however, than may be noted in the initial chill of an acute infection—in fact, the reaction is of the same character.

Following the injection, there is a leukopenia, due to reduction of the polynuclear cells. With the onset of the chill, there is a gradually increasing leukocytosis, which reaches its maximum in four to nine hours. There is little, if any, relationship between the degree of leukocytosis and the beneficial results.

Mention has been made of the various agents in non-specific therapy. Müller and Thanner's early use of milk in parenchymatous keratitis has led to the use of this agent by other ophthalmologists. Of the various non-

specific agents on the market, none, I believe, are toxic in the sense of tissue injury. Mercurochrome, outside of urinary tract infection, is probably a non-specific remedy. As it is highly toxic, its application should be limited to this special field.

Dosage.—*Milk.*—The dosage of only two non-specific agents will be discussed, *i.e.,* milk and typhoid vaccine. Fresh or pasteurized milk is boiled or, as some advocate, allowed to simmer for ten minutes and then cooled. It is never to be injected intravenously. The initial dose is 2 to 5 c.c., given intramuscularly, the dosage to be increased with subsequent injections. Rarely does the amount given in a single injection exceed 10 c.c. The interval between treatments varies from two to four days. The total course does not usually exceed five injections. It is the writer's opinion that if no improvement is noted after two or three reactions, the treatment should be discontinued, as improvement usually appears very promptly. If there is improvement after each injection and the maximum amount of benefit is not obtained after five treatments, more may be given. However, failure to improve is an indication for discontinuing the treatment.

Within five to six hours after the injection, there is a chill or at least a marked rise in temperature. The reaction resembles that observed after other foreign proteins. The results are comparable with those obtained with intravenous protein therapy. The reaction is frequently less violent than that observed after typhoid vaccine, and this is considered by some as an advantage. In children or obese individuals, it is certainly much easier to administer than typhoid vaccine. There is one slight objection to milk—the danger of an anaphylactic reaction in a sensitized individual. The fear of sensitizing to milk as a result of treatment is unwarranted.

Typhoid Vaccine.—The dosage of typhoid vaccine varies, with different observers, from 25 to 250 million, the objective being to secure a good reaction and at the same time avoid violent reactions with nausea and vomiting. While severe reactions can scarcely be considered dangerous, they inconvenience the patient and may make him loath to continue the treatment. It is impossible to name a dosage that will always give a satisfactory reaction, as there are marked individual variations. The same patient may react quite differently to the same dose when repeated. There is evidence that a severe reaction will give results that cannot be obtained with a moderate reaction.

The writer in recent years, when treating a chronic infection like chronic arthritis, has been accustomed to give 25 to 35 million as the initial dose, increasing each succeeding dose by 10 to 15 million. This increase is necessary in order to obtain a good reaction. The interval between injections is largely arbitrary. Formerly, the treatment was repeated every other day. As the method of action is thought to be a mobilization of immune bodies, the interval has been lengthened to permit of the accu-

mulation of antibodies. The writer repeats the treatment every fourth day.

How long shall the treatment be continued? This depends upon the patient's reaction to the treatment. In chronic arthritis, if no benefit is noted after two or three injections, it is highly improbable that further treatment will avail, and it is unnecessary to subject the patient to the inconvenience of a reaction. As long as further improvement follows the injections, they should be continued. Rarely is it necessary, in chronic arthritis, to give more than five treatments. If within a few days or weeks after completing the treatment, the patient should show evidence of recurrence, further treatment may be tried. In the writer's experience, continuing the treatment after the maximum improvement has been reached does not prevent recurrences.

The above method of treatment is that employed in chronic and acute arthritis. The method employed in other infections will be described under the discussion of these special diseases.

Dangers.—Is foreign therapy dangerous? The writer has administered or supervised the administration of foreign protein to several hundred patients during the past twelve years, without a fatality directly due to the treatment. One patient, an alcoholic with arthritis, developed delirium tremens and then pneumonia following treatment, and died. This is the only fatality traceable indirectly to the reaction. Chronic alcoholism may be considered a contra-indication, as the development of delirium tremens is not unusual, resembling in this respect the reaction of this group of patients to any acute infection.

The writer has never observed an anaphylactic reaction following typhoid vaccine, although not infrequently there may be an interval of ten days or more between injections. Elderly individuals with evidence of impaired myocardium, or those with marked hypertension, have not been treated. The same holds true of patients who have suffered for a long time from an exhausting infection. Subacute bacterial endocarditis has not been treated, but a compensated valvular lesion is not a contra-indication. With proper dosage and selection of patients, foreign protein is not a dangerous therapeutic agent. Failure to observe these precautions may lead to serious consequences.

Autohemotherapy.—Before discussing the use of non-specific agents which produce a reaction, it might be well to consider some non-specific methods claimed to have therapeutic activity without causing a marked reaction.

Blood after clotting behaves as a foreign protein to the host. After separation of the serum from the clot, the former may be injected intravenously, subcutaneously or intramuscularly. The whole blood, citrated or untreated, may be given subcutaneously or intramuscularly. When the serum is given intravenously, it not infrequently excites a febrile reaction.

When serum or whole blood is given subcutaneously, there is at most only a very slight rise in temperature, although there may be considerable leukocytosis, at times preceded by a leukopenia—in other words, a miniature foreign protein reaction. The dose is 1 to 3 c.c. of serum intravenously, or 10 to 50 c.c. of whole blood intramuscularly.

Judging from the rather extensive literature, normal serum therapy has some value. The results on the whole are less striking than those observed after protein shock therapy. The absence of reaction permits its use in certain cases where a chill is undesirable. The author's experience with normal serum is limited to the use of immunized and normal chicken serum in pneumonia. Here the results are apparently dependent upon the temperature reaction. If the patient reacted with a chill, the disease might promptly terminate by crisis. When there was no febrile reaction following the injection, there was no apparent improvement.

Kraus and his colleagues claim good results from the use of normal beef serum in human anthrax. Bingel, during the late war, when it was difficult or impossible to secure diphtheria antitoxins, used normal horse serum on alternate patients with diphtheria. Diphtheria antitoxin was administered to 471 patients; normal serum to 466. The mortality was the same in the two series. Calhoun claims that 1 c.c. of normal horse serum has the same protective action as six units of diphtheria antitoxin. Three of these units can be accounted for by antitoxin normally present in horse serum, and three units due to a non-specific reaction.

Moog, Rhode and Schultz treated a limited number of scarlet fever patients with intravenous normal serum, claiming results closely approximating those obtained with convalescent serum. Rhode reports good results in pneumonia after the subcutaneous injection of 50 to 60 c.c. of the patient's blood. In case there was no improvement at the end of twelve hours, he injected 1 to 2 c.c. of defibrinated blood intravenously.

This form of treatment has been employed most extensively in dermatological conditions. Salutzki and Weiss have recently reported their experience, and those interested in this subject will find an adequate list of references at the end of this chapter. They report excellent results in acute eczema, and satisfactory results in acne vulgaris, sycosis simplex and trichophytosis corporis. This form of treatment, on account of its simplicity and reported good results, deserves further study. Daily 10 to 20 c.c. or more, of freshly drawn blood may be injected; if serum is used intravenously, 2 to 3 c.c. may be administered.

CLINICAL APPLICATION

Acute Arthritis.—Non-specific therapy has been used more extensively in arthritis than in any other disease. In acute arthritis, the results are often dramatic. A helpless patient within two or three hours after the

reaction may be quite comfortable. About 70 per cent of patients with acute arthritis are practically free from discomfort after two or three injections of typhoid vaccine. In about 35 per cent of these the relief is permanent, indicating complete destruction of the infection. In the others, following an interval of a few days to several weeks, the arthritis returns. In these, the infecting agent has not been entirely destroyed. Reappearance of the disease several weeks after treatment may be due to reinfection. The writer has endeavored to eliminate these relapses by giving several treatments after the patient has apparently recovered, but without success. Experience suggests that it is difficult or impossible to completely immunize every patient.

The method of treatment is the same as in chronic arthritis. The patient receives an initial injection of 25 to 35 million typhoid bacilli. If there is a good reaction, the patient is given, after the lapse of four days, 35 to 40 million, and each successive dose is increased by 10 to 15 million, or enough to give a good reaction. In case the patient continues to show improvement, the treatment is continued until all symptoms have disappeared or the progressive improvement ceases. In case of relapse, treatment is repeated with the first evidence of return of symptoms.

In case no improvement is noted after two reactions protein therapy is discontinued, as only rarely will further treatment be beneficial. In some of these apparent failures, if, a few days after treatment has been discontinued, the patient shows marked improvement, further treatment may be tried.

Protein therapy is of value in acute arthritis, and is apparently the only means of aborting the disease. It does not lessen the frequency of endocardial involvement.

Chronic Arthritis.—On the whole, the results of non-specific therapy in chronic arthritis do not create much enthusiasm. If patients are carefully selected, worthwhile results may be obtained in a limited number of cases. The more recent the onset and the greater the evidence of activity, the better the prospects. Needless to state, the treatment is futile in chronic osteo-arthritis in the absence of evidence of active infection in the joints. Chronic arthritis of the atrophic type, of less than a year's duration, where only a few joints are involved may be benefited by this treatment. This is the type which is believed to be due to an infection. The hypertrophic type with exostoses may be largely traumatic in origin. A considerable number of patients, with the characteristic spindle-shaped finger deformity of atrophic arthritis, with a history of acute or subacute onset, may be entirely freed from the arthritis, or at least the infection eliminated, and with the aid of heat and massage, the joints may be restored to a high degree of usefulness. In chronic hypertrophic arthritis, where there is evidence in some joints of subacute inflammation, protein therapy may relieve this active process. Mono-articular gonorrheal arthritis, of months'

standing and with very marked stiffening of the joint, may yield in a remarkable manner to the treatment. The writer has seen a wrist edematous and almost rigid clear up after two or three injections. Needless to say, in such a case only the periarticular structures are involved. Patients with osteo-arthritis of the spine frequently suffer from neuritis. Non-specific therapy is of no value here. The above discussion is based on the author's personal experience. Some physicians are much more optimistic, others are less so.

Yeoman recently reported a series of fifty cases of subacute and chronic arthritis, with improvement in from 80 to 90 per cent. In 50 to 60 per cent of these the improvement was maintained. He states correctly that the subacute type, where the disease is confined to the periarticular structures, is the most helpful.

Stockman and Campbell report a series of seventy-three cases, both acute and chronic, with forty patients permanently benefited. They obtained the best results in those cases of chronic arthritis where the disease began in an acute form. When the onset was insidious, if any improvement was noted, it was usually only temporary. Fliegel and Strauss report a series of patients with chronic arthritis treated with mirion, a proprietary preparation, with 50 per cent of cures. Biencke, using this same preparation, reported 25 per cent of cures. He states that there is no relationship between the presence or absence of a reaction and improvement in the patient. The writer has used mirion and has only noted relief when a reaction took place.

Pneumonia.—The value of non-specific therapy in this disease is of special interest, as it raises the question whether the favorable action of so-called specific serums and antibody solutions are due to their specificity. Leaving out of the question the possibility of benefit without febrile reaction, it has not been determined satisfactorily whether patients who have a febrile reaction after serums are more apt to be benefited than those who do not react.

That the course of a pneumonia may be modified following a protein reaction, is established. Lüdke noted an immediate improvement in five out of ten cases of pneumonia following the intravenous injection of 1 to 3 c.c. of a 10 per cent proteose. Von Velder and Pitz, and Münzer have reported definite results in bronchopneumonia following the intramuscular injection of milk. Gardner-Medwin has precipitated a crisis in pneumonia with subcutaneous injections of sodium nucleinate. This does not by any means exhaust the literature on this subject. The writer treated fifteen consecutive cases of lobar pneumonia, within forty-eight hours of the onset, with a single intravenous injection of typhoid vaccine. In three of these there was an immediate lasting crisis.

Keyes' immunized chicken serum lowered the mortality in pneumonia in a well-controlled series of cases. A chill or marked febrile reaction

often followed the injection. The serum was later modified by removing the fibrin, which in a large measure eliminated the reaction, and at the same time destroyed the curative effect of the serum.

Any benefit derived from Huntoon's Antibody Solution was probably non-specific, as large quantities introduced subcutaneously and without reaction had little if any effect in controlling the disease.

The development of a violent reaction in pneumonia is not free from danger. After obtaining the above-mentioned information on fifteen cases, the writer discontinued its use, although no bad effects were observed. Shock therapy in pneumonia, however, is not free from danger as shown by Connor and Cecil, and it is not to be recommended.

Some interest has been developed in the use of mixed vaccines given subcutaneously in pneumonia. The writer has never used this form of treatment, but has studied the temperature curves in treated cases. There is evidence that this modifies somewhat the course of the disease and apparently lowers mortality. Marked temperature reactions do not occur, and, on the other hand, early crises are not noted. As stated previously in this paper, dramatic results are only noted after a reaction. Less dramatic benefit, however, may follow the safer subcutaneous or intramuscular use of foreign protein.

Typhoid Fever.—Attention has already been called to typhoid as the disease where the effectiveness of non-specific therapy was first demonstrated. Since then, there has developed an extensive literature clearly demonstrating that the course of the disease can be modified even to immediate termination. It is also claimed that the mortality is lowered. Approximately 20 per cent of cases terminate by crises following a single reaction; 20 per cent more by rapid lysis; in another 20 per cent the fever becomes irregular, the severity of the disease lessened and its course shortened. The course of the disease is not modified in the remaining 40 per cent. Accepting the present theory of action, this last group either does not have available antibodies or the reaction fails to mobilize them.

As in pneumonia, the treatment is not free from danger. Even small doses of typhoid vaccine—15 million bacilli—may produce a violent reaction. The writer has treated typhoid by this method and observed the dramatic sudden termination of the disease and has never seen any ill effect. However, a temperature reaction of 108° F. gives rise to uneasiness and the physician's responsibility is too great. Those who have the courage to try it should use a very small dose of typhoid vaccine. A safer method of treatment is to give large doses intramuscularly, enough to excite a good local or a moderate general reaction. Holler has used very small doses of proteose intravenously, just enough to excite a very mild reaction. In the beginning he gives two treatments daily; later one injection, continuing this until the fever subsides. In 1917, he reported 350 cases treated by this method, with a mortality of only 0.5 per cent, and an average dura-

tion of the disease of only ten days. He employed a 10 per cent solution of deutero-albumose, beginning with 1 c.c. and gradually increasing the dose but avoiding a reaction.

Puerperal Sepsis.—One would scarcely think that a condition like sepsis, frequently accompanied by chill, would be benefited by protein therapy. Nevertheless, there are many advocates of this method of treatment. Reference will be made to a few of the many reports in the literature. Lüdke treated five cases with three rapid recoveries. Wilmette reports a series of cases of puerperal sepsis with good results, several terminating by crisis. Jacob and Wendt treated seven patients with sepsis by the subcutaneous injection of turpentine, causing a localized abscess. They are quite enthusiastic about this treatment, and believe it is frequently a life saver.

Erysipelas.—Apparently, non-specific therapy may be used to advantage in this disease. Petersen reported a series of fifteen cases treated with albumose, milk or typhoid vaccine, with striking results in some of the cases. He refers to fifty-two cases treated by Schmidt with milk injections. In twenty-seven of these, defervescence began within twenty-four hours, and in twelve more within three days. There are numerous other reports in the literature, all indicating some degree of benefit. The earlier the treatment is begun, the better the results.

Gonorrhea.—Gonorrhea and its complications have received considerable attention from those interested in non-specific therapy. It has long been recognized that an acute intercurrent infection may favorably influence an acute gonorrhea. Typhoid vaccine has been used in the arthritides of gonorrheal origin. According to Keyes, favorable results are secured by large doses, but at the risk of severe reactions. In epididymitis excellent results have been noted. Less striking improvement has been noted in tubal infection.

Bacillary Dysentery.—This very stubborn disease is reported to yield to non-specific therapy. It is generally conceded that treatment with specific serum is far from satisfactory. During the late war, non-specific treatment was quite extensively used. Nolf, who found specific serum subcutaneously of little value, resorted to intravenous administration. This gave the characteristic non-specific reaction and very good results. Lüdke treated twenty cases (thirteen Shiga and seven Flexner) with albumose, with five rapid recoveries. Many other references might be given, all testifying to the value of non-specific therapy.

Encephalitis.—Dannhauser reported good results in acute encephalitis. Liener's results in postencephalitic mental changes are most interesting. His attention was attracted to this treatment after observing a recovery following pneumonia. He reported gratifying results in twenty-three patients.

Ophthalmology.—Non-specific therapy, especially in the form of milk injections, has been used extensively in iritis, keratitis, choroiditis and

conjunctivitis. Müller and Thanner noted good results in all these conditions, and especially satisfactory results in acute iritis. Jacovrides treated 150 corneal ulcers, 140 of which were cured after two or three injections. Huber, after observing that trachoma was greatly benefited after recovery from scarlet fever, treated a series with milk and was well pleased with the results. Non-specific therapy has been highly commended in specific ophthalmia. In the writer's experience, there is no acute infection in which the results are so uniformly good as in acute iritis. The relief is usually prompt and permanent.

Dermatology.—Shock therapy has been used with reputed good results in dermatitis, pruritis, ringworm and lupus.

Syphilis.[1]—Wagner-Jauregg's treatment of paresis has created a new interest in non-specific therapy. When its syphilitic origin was definitely determined, it was hoped that antisyphilitics might be beneficial, but they proved to be of little if any value.

Long before the etiology of paresis was understood, it had been observed that following a severe infection the patient often showed marked improvement and in a few instances permanent cure. In 1802, Halban collected a series of "cured" paretics, the majority of whom had previously had some severe acute infection or prolonged suppurative process. Gerstmann states that both Boerhaave and Sydenham had noted the beneficial effects of fever in psychoses. Kostel, in 1856, reported improvement in psychoses following smallpox, and Schlager, in 1857, after typhoid fever. Schlager stated that six of eleven patients in an institution, who had typhoid, were cured.

Schroeder Van Der Kolk, in 1863, reported the recovery of an insane patient following measles. Nasse, in 1870, reported ten out of twenty-one mental patients cured following typhoid, and five temporarily benefited. Rosenblum, in 1874, reported four psychoses greatly improved after intermittent fever, and one following typhoid fever. He also states that psychoses inoculated with recurrent fever were greatly benefited. Fleming, in 1877, reported a seven-year remission in a paretic following typhoid. Gerstmann discusses many other instances of recovery in mental disorders following acute infections. Whether all mental cases that recovered had paresis cannot be determined.

Wagner-Jauregg became interested in this subject very early and, in 1887, published an article on "The Action of Febrile Diseases on Psychoses." Since this time, he has persistently studied this subject, using various means for exciting fever. His faith in the possibilities of this form of treatment is admirable. He first tried tuberculin in small doses, later in amounts sufficient to give a temperature reaction. With the reaction doses he obtained some "lasting" remissions; the patients were able to return to work. Later, he used Besredka's polyvalent typhoid vaccine.

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[1] See also the article by Bunker in this volume.

This contained living typhoid bacilli, their virulence reduced by mixing with typhoid immune serum. This vaccine was given intravenously, beginning with 25 million and gradually increasing to 250 million. The injections were repeated every second day until eight to twelve had been given. The frequency, degree and duration of the remissions were much better than with tuberculin.

Wagner-Jauregg inoculated his first patient with malaria in 1917. In 1919, he reported on nine cases. Four of these were greatly improved, and two of them, in 1925, were working at their former callings. The other two improved patients later relapsed. Since 1917, he has used malaria almost exclusively in the treatment of paresis. By 1925, he had treated 1,000 cases. His report was of especial interest, as practically every paretic was treated and not merely selected cases. In his earlier work he treated only selected cases. His results have recently been presented in monograph form by Joseph Gerstmann. In this report, he includes only the 400 cases treated previously to 1924. Thus all these had been under observation from two to six years after completing the treatment. Following, or associated with the malaria treatment, the patient received six injections of neo-arsphenamin. There were 132 patients (31 per cent) who had complete remissions, and had returned to their previous occupations, being able to carry on in a normal manner; fifty-seven had incomplete remissions, were able to leave the institution and return to work, but not to their previous callings.

The patients are allowed to have about sixteen to eighteen chills, then the parasites are destroyed with quinin. The mortality from the treatment is high—10 per cent. A decided factor in the mortality is the marked anemia due to the malaria. At present, in some clinics they are interrupting the treatment by giving quinin after six to eight chills, and when the patient has recuperated, he is reinoculated with malaria.

Typhoid vaccine has an advantage over malaria, inasmuch as one can regulate the frequency of the chills, depending on the patient's condition. Hall, Kunde and Gerty have been treating paretics with typhoid vaccine. By gradually increasing the dose, they are always able to get a good reaction. The final maximum dose may reach 2 billion. No serious complications have been noted after these massive doses. If time should show that the results are comparable with those obtained with malaria, this method, on account of its simplicity and safety, might be adopted.

Apparently non-specific therapy has a decided action in early spinal lues. In Finger's clinic, when the spinal fluid was positive in early syphilis, they found malaria the most efficient method of rendering it negative.

Tabes Dorsalis.—Wagner-Jauregg is not enthusiastic over the malarial treatment in tabes, although he reports disappearance of the lightning pains and crises.

Multiple Sclerosis.[2]—The etiology of multiple sclerosis has not been definitely determined. There is, however, an increasing tendency to look upon it as infectious in character. If so, non-specific therapy might be beneficial. Gross, a student of Wagner-Jauregg, treated one series of cases with typhoid vaccine, and another series with malaria. The typhoid series included twenty-nine patients of the chronic progressive type, none of whom had shown any tendency to remission; 27 per cent showed very marked improvement. In the series treated with malaria, forty-two patients—26 per cent of the acute type and 16 per cent of the chronic progressive type—were greatly improved.

Schacherl treated sixty-four patients with a combination of neo-arsphenamin and typhoid vaccine with 62.5 per cent definitely improved.

Dreyfus and Hanan have treated two series—one with malaria, the other with typhoid vaccine—with somewhat better results with malaria.

This is a new field in which non-specific therapy offers some hope. If the disease can be brought to a standstill, it will mean much. If the treatment is begun early, before irreparable tissue changes have developed, complete recovery is possible. As a rule, sixteen to twenty injections are given at two-day intervals. It is advisable, in case the patient shows marked improvement, to give, after the lapse of three months, another series of eight to ten injections.

Gastric and Duodenal Ulcer.—At first thought it would appear highly improbable that protein therapy would be of value in peptic ulcer. If we accept the view that such ulcers are of bacterial origin, this treatment is not illogical. It appears from the literature, that not only may ulcer symptoms promptly disappear, but in some cases at least the ulcer may actually heal. Whether this should be accepted as evidence, that peptic ulcer is of bacterial origin does not necessarily follow. Pribram and others have reported very interesting series of cases treated by this method, using a vegetable protein. It is quite improbable that the character of the protein is significant. The patients were kept on a general diet, without addition of alkalis. He reported 300 cases and stated that, with few exceptions, the pain was at least temporarily relieved after a few injections. Good results were obtained in 50 to 60 per cent of cases. The treatment was given at two- to four-day intervals, the patient receiving a total of eight to ten injections. A dose of 10 to 15 millions of typhoid vaccine, sufficient to give a mild reaction, is all that is required. Holler and Perutz have confirmed Pribram's results. Recurrent hemorrhage is a contra-indication. The writer has tried their treatment in a few patients, solely for the purpose of determining whether it would relieve the discomfort. In several stubborn ulcers with marked discomfort, after a few injections of typhoid, the pains disappeared, although the patient was on a ward diet and with-

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[2] See also the article by Young and Bennett in this volume.

out alkalis. A further carefully controlled study of this treatment may show that it is well worth while.

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CHAPTER III

BACTERIOPHAGE THERAPY

George H. Smith

GENERAL CONSIDERATIONS

Whatever may be the interpretation as to bacteriophage—its origin, the mechanism of its action, its biological significance, and its intimate nature—the fact remains that this intangible something, bacteriophage, appears to be finding a place among those agents successfully used in the prophylaxis and therapy of infectious disease.

Several hypotheses as to the nature of bacteriophage have been advanced, but as yet none have been proved through any direct method of experimentation, and, indeed, from the standpoint of the practical use of bacteriophage in therapy, it makes but little difference, save in the interpretation of the mode of action.

The theory of d'Herelle conceives bacteriophage to be an autonomous being, ultravisible and filtrable, a virus parasitic of bacteria, and because of its parasitic nature, under suitable circumstances destructive to its host. Bordet regards bacteriophage as the manifestation of an abnormal autolytic tendency on the part of the bacterium, referable to a disturbance in the assimilative and metabolic activities of the bacterial cells. Hadley would have us consider bacteriophage as merely a phase of bacterial cyclogeny, closely associated with the phenomena of microbic dissociation. Many other hypotheses have been suggested, most of them involving directly or indirectly some of the ideas expressed above. But, although the crucial experiment has yet to be devised to solve this problem, all theories recognize, with difference in emphasis, the chief manifestations of bacteriophagic activity.

Bacteriophage is, to all intents and purposes, particulate in nature, existing either as corpuscles representing the active agent itself, or as something in less definite form adherent to or adsorbed by corpuscles. Filtration experiments would indicate that these corpuscular elements are approximately 20 to 30 micra in size. They are susceptible to the influence of centrifugal force, and bear a negative electrical charge. Being ultramicroscopic, the presence of these corpuscles can be demonstrated only through evidence of their characteristic activities and, consequently, a study of bacteriophage resolves itself into a consideration

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of the conditions which favor or inhibit the phenomenon of bacteriophagia and the results attendant thereto.

Various determinations have been made of the influence of chemical agents and of physical forces upon bacteriophagic activity, the results showing that its activity as a lytic agent is impaired or totally inhibited by most of the germicidal agents as well as by heat. To all of the chemical bactericidal agents, save those, such as glycerol, which are relatively inert on viruses, bacteriophage is relatively susceptible. To heat, its resistance varies somewhat with the preparation under study, but generally speaking bacteriophage is rendered inert by exposure to temperatures between 65° and 75° C. Irradiation weakens and finally completely inactivates the principle. It resists aging, although attenuation occurs.

To body fluids, with the exception of bile, bacteriophage is insensitive, provided the concentration used does not decidedly alter the viscosity of the medium in which it is acting. Glandular extracts and enzymes, as a rule, seem to be inert, but bile, although not destroying bacteriophage, clearly inhibits its activity, a fact of possible importance in connection with the behavior of bacteriophage in certain infectious diseases. With most, if not all, preparations of bacteriophage, an alkaline reaction is essential for activity. From the broader standpoint it may be said that bacteriophage is most potent and shows the highest degree of activity under those conditions which are most favorable to the vital activities of the bacterium upon which, or with which, it is acting.

As regards the chemical constitution and chemical activities of bacteriophage, little is known beyond the fact that it seems to be protein in nature, a conclusion based upon the fact that bacteriophage is antigenic, leading, when administered to an animal under suitable conditions, to the production of an antibody which is inhibitory to the most characteristic action of bacteriophage, the lytic phenomenon. Many races of bacteriophage, perhaps all, yield, either as a metabolic product or as a derivative of disintegration, a lytic principle capable of acting upon bacteria, effecting a dissolution even in the absence of the corpuscular elements.

Bacteriophage is to be found, under normal conditions, with great uniformity within the intestinal tract of man and animals. Naturally, being excreted it is to be found also in material subject to fecal contamination, and it has been isolated repeatedly from water, soil, and sewage.

While under normal conditions bacteriophage seems to be confined to the intestinal tract, under abnormal conditions it may appear elsewhere in the body, and under various circumstances it has been recovered from the blood stream, from the pleural and peritoneal cavities, from subcutaneous tissues in localized infections, from the mouth, the vagina, the bladder, the kidney, and other organs.

Apparently it is not present in the body at birth, for various studies

show that it can first be detected in the intestine some four to seven days after birth. Thenceforth, throughout life it is uniformly present, although at different times its potency and its range of activities present very great variations.

Thus far it has been impossible to demonstrate bacteriophage or to produce it out of association with living cells—bacteria. Hence, for its demonstration and isolation, living, normally growing bacteria are essential. But bacterial strains are not all alike in their ability to regenerate bacteriophage. Not only is there an element of species specificity involved, but even within certain bacterial species, some strains, indeed, probably some individual bacterial cells, are quite incapable of serving in the production of bacteriophage. This incapacity may be a natural attribute or it may be a developed tendency, such cells being insusceptible to the action of bacteriophage, having a resistance, either natural or acquired. Other strains or species are naturally sensitive and readily undergo the transformations brought about by bacteriophage, thereby serving in the regenerative phenomenon. This fact of resistant bacterial types is of fundamental importance from the standpoint of the application of bacteriophage to therapeutic purposes, since with resistant strains bacteriophage seems to be inert from all standpoints.

Perhaps of greater importance is the fact that under a variety of conditions the exposure of fully sensitive cells to bacteriophage results in a transformation of bacterial type, converting them into a bacteriophage-resistant strain. Such a change occurs when excessive numbers of bacteria are exposed to bacteriophage, even though the bacteriophage be highly virulent, or when bacteria come into contact with a bacteriophage of low virulence.

The element of specificity also enters into the problem of therapy, for it is essential to bear in mind the distinctive behavior of certain bacterial species. Within some species individual strains or cultures possess attributes which determine behavior, while in other species behavior is governed by characteristics which are species-specific rather than strain-specific. Thus, in the absence of an acquired resistance to bacteriophage, all strains of *B. dysenteriæ* Shiga exhibit bacteriophage phenomena with any race of bacteriophage active for any strain of this organism. Such a species is homogeneous. With *B. coli* and the staphylococcus, for example, such uniformity of behavior does not obtain, for a given strain of staphylococcus may be highly sensitive to one race of bacteriophage and completely refractory to another, even though the latter is highly potent in its action upon another strain of staphylococcus. Such bacterial species are heterogenic, factors of strain specificity transcending any common attributes referable to species.

As a further consideration mention should be made of the fact that many, perhaps most, races of bacteriophage are not restricted in their

activity to but a single species. They have, as might be said, a "major virulence" with which are associated "minor virulences"; for example, a single preparation may act very vigorously upon *B. coli,* and at the same time less intensely upon *B. typhosus* and *B. enteritidis.*

Thus far "races" of bacteriophage have been isolated active for many of the bacteria pathogenic for man—including *B. typhosus* and the paratyphoids, *B. dysenteriæ* strains, members of the *B. coli* group, streptococci, staphylococci, the gonococcus, *B. pestis, Vibrio choleræ,* and *B. diphtheriæ.*

The great diversity of these strains strongly suggests that they are but examples of a general law; that probably races of bacteriophage may be found active for all bacterial types.

As a rule it is extremely easy to procure a "race" of bacteriophage, the most satisfactory source being fecal material and the best organisms for revealing its presence being either *B. coli* or *B. dysenteriæ* Shiga. For isolation a portion (2 to 5 grams) of feces is introduced into 50 c.c. of alkaline extract broth (P^{II} 7.6), allowed to incubate for twelve to twenty-four hours, and then subjected to filtration through a Berkefeld candle or other filter of that type. The filtrate, containing bacteriophage, may show an extreme activity or may be but weakly active; it may be active for several bacterial species or may react upon only one. Activity can only be demonstrated by combining the filtrate with a suspension in alkaline broth of a young (eighteen to twenty-four hour) culture (washed from solid media) of some susceptible bacterium, preferably *B. coli* or *B. dysenteriæ* Shiga.

Manifestly if races of bacteriophage possessing other activities are sought, such as a staphylococcus bacteriophage, other materials, as pus, must be examined, and an appropriate test organism employed.

Where such a mixture is incubated, the result will be readily detected if the filtrate contained a highly or moderately potent bacteriophage. An inhibition of bacterial growth or a clearing of the turbid culture takes place. When transferred to agar, material from such a tube yields no growth whatever or but shreds of bacterial culture will appear scattered over the plate. When the bacteriophage is still less potent, the layer of bacterial culture will appear studded with circular areas, plaques, devoid of bacteria.

In cases where the broth tubes completely clear, the dissolution may be permanent, indicating a highly virulent bacteriophage, or after a variable period (a few hours to several weeks), the medium may again become clouded (bacteriophage races of lower virulence) with the development of resistant bacteria.

With bacteriophage races of low potency, the bouillon tubes may be macroscopically indistinguishable from the control culture, and only the development of plaques upon the solid medium affords any assurance

that bacteriophage is present in the filtrate. With such weak races of bacteriophage, it is usually possible to build up "virulence," and this can be accomplished by making serial contacts with the sensitive bacterium, combining each successive filtrate with fresh bacterial suspension.

The question of potency or "virulence" of bacteriophage is of the greatest importance from the point of view of therapy, since, as stated above, the exposure of fully susceptible bacteria to a bacteriophage of low virulence may convert this sensitive bacterium into one which is resistant and refractory to all races of bacteriophage whatever their potency. A race of bacteriophage can hardly be termed "virulent" unless, in an amount of 0.000001 c.c., it causes a complete and permanent dissolution of a bacterial suspension containing 250 million to 1,000 million bacteria per cubic centimeter, the absolute number depending upon the bacterial species. Only such races should be used for therapeutic purposes.

BACTERIOPHAGE AS A THERAPEUTIC AGENT

The use of bacteriophage as a therapeutic agent in human infections is based primarily upon two observations: First the behavior of the principle under natural conditions in infectious disease in the individual and during epidemics; and, second, upon the laboratory demonstration of the changes brought about in bacteria by exposure to bacteriophage. Studies along both of these lines give grounds for believing that, could the conditions be made suitable, bacteriophage should play a determining rôle in infectious processes.

As to the latter of these two points, it must be confessed that as yet we have no very clear concept of the mode of action of bacteriophage in its relation to an infectious process *in vivo*. That in some circumstances it is effective cannot be questioned, but certainly it is not entirely clear as to what mechanisms are involved; *in vitro* at least, bacteriophage causes a destruction or dissolution of those bacteria susceptible to its action. If a similar effect is exerted *in vivo,* a fact which cannot yet be demonstrated beyond question, its effectiveness may well be ascribed to a direct destructive influence. Further, bacteriophage has been shown to exert a decided opsonic effect, at least *in vitro,* markedly stimulating the phagocytic activity of the polymorphonuclear cells. If a like influence is exerted *in vivo,* and particularly if the action extends to the phagocytic cells of the reticulo-endothelial apparatus, the effect of bacteriophage may be in large part phagocytic. Again, bacteriophage most certainly detoxicates toxic bacterial proteins, and possibly this activity also may be of importance in modifying sensitivity to the proteins of products of bacteria, and thus indirectly exerting an influence upon susceptibility to or recovery from disease.

Although attempts have been made to utilize bacteriophage in the

treatment of many types of infection, in only a few instances have the conditions governing the work been sufficiently controlled to justify the hope of satisfactory results. Much of the work was done before the nature of the processes of bacteriophagia was understood, before the importance of virulence in bacteriophage races was appreciated, before the question of resistant bacterial strains had received adequate attention, before the limits of the specificity of action were defined, and before it was known that bacteriophage is antigenic and when injected engenders antibodies inhibitory to its action. Furthermore, methods of administration, quantities given, intervals between treatments, etc., have had to be determined and certainly optimum conditions were not provided in all instances. Indeed, it is certain that the methods now employed are in many cases susceptible to improvement.

Possibly these factors, perhaps other more basic and even less well-understood principles may have been responsible for the failure of many of the attempts at bacteriophage therapy. But, however this may be, certain it is that in certain types of infectious disease treatment with bacteriophage has given results, at least equal to those attained with any known method of biologic therapy.

Infections Due to Bacilli of the Enteric Group

B. Dysenteriæ.—Bacillary dysentery, the first of the infectious diseases of man to be successfully treated with bacteriophage, may well receive attention first, particularly since in this infection the value of this mode of treatment is most firmly established and because the therapeutic procedures herein developed have served to guide treatment in other infections and to disclose what is known about the mode of action of bacteriophage. It may perhaps be unfortunate that therapeutic procedures have throughout been patterned after those which have proved most efficacious in this disease, for certainly, infections such as typhoid fever or pyogenic infections of the kidney may well require distinct and special modes of treatment, even though the therapeutic agent—bacteriophage—possesses the same fundamental attributes in all instances.

B. dysenteriæ represents a homogeneous species as regards its behavior toward bacteriophage; that is, all naturally susceptible strains of dysentery bacilli are acted upon by a potent bacteriophage which is active for any one strain. Manifestly, as regards therapy, this implies (an implication which does not extend to other infections) that the derivation of the bacteriophage is of no importance; the autogenous factor or element of strain specificity need not be considered. It is, however, of the utmost importance that the virulence be extreme, *i.e.,* of such degree that a *complete* and *permanent* dissolution of a turbid bacterial suspension occurs when but a minute quantity (0.00001 c.c. or less) of the bacteriophage

filtrate is added. With such a filtrate administrations may be given by mouth, by injection, or by a combination of both. Thus far it has been impossible to demonstrate any harmful effects from the ingestion of bacteriophage, whatever its titer, range of virulence, or whatever the amount taken. Generally speaking this has also been the experience of most of those who have injected bacteriophage, although some few workers have reported reactions usually local rather than systemic, referable to the injection. Needless to say, bacteriophage treatment should be instituted as early in the disease as possible.

The procedure adopted by those who have worked most extensively with dysentery, consists in giving 2 c.c. of highly active bacteriophage by mouth. The age of the bacteriophage preparation is of no moment so long as it is of maximum virulence. In this connection it should be noted that most races of bacteriophage become somewhat attenuated with aging, different preparations showing considerable variation in their ability to retain potency, and since no limits can now be assigned to the rate of deterioration or the duration of activity, old filtrates (more than six months) should not be employed without preliminary tests of potency. Naturally, freshly cleared, unfiltered or filtered preparations should not be used until a period of incubation or aging insures against the development of resistant secondary cultures.

Experience has shown that in those cases where bacteriophage treatment is to prove effective, evidences of a remission of symptoms become apparent within eight to twelve hours after the initial treatment. Not only is the number of stools diminished and their character altered, but bacteriological studies of the intestinal flora reveal a prompt reduction in number or a complete disappearance of dysentery bacilli. Filtrates prepared from such stools show that the potent bacteriophage has become implanted in the intestine. In cases that do not respond promptly, a second administration should be given within an interval of forty-eight hours. A few cases of bacillary dysentery have been treated by the direct introduction of bacteriophage, by duodenal tube, into the intestine. Where this method has been adopted, 30 c.c. of bacteriophage filtrate has been given on each of two occasions, with an interval of a week, but the results reported appear to be in no way superior to the far simpler oral administration.

The literature affords reports based upon the treatment of many thousands of cases of bacillary dysentery, and the conclusion cannot be avoided that in general the results attained are far superior to those attending any other therapeutic procedure. It is needless to add that in isolated instances the results have been unquestioned failures, referable, in some instances at least, to failure to establish bacteriologically the etiological agent of the infection, or to utilize in treatment a preparation of adequate potency.

B. Typhosus and the Paratyphoid Bacilli.—From the apparent close relationship bacteriologically of these organisms to *B. dysenteriæ,* it might reasonably be expected that as regards behavior toward bacteriophagia they would be similar. Such is not the case.

Unlike the dysentery strains, typhoid and paratyphoid bacilli belong to heterogenic species. This means that a given preparation of bacteriophage may be highly active for a certain strain of *B. typhosus* and at the same time wholly inert for another typhoid strain, even though the latter be fully susceptible to another bacteriophage preparation. Manifestly this imposes an added obligation in attempting bacteriophage treatment of these infections, for it becomes essential to demonstrate not only activity of bacteriophage for typhoid bacilli but a specific activity for the strain in question. A laboratory preparation of typhoid bacteriophage may or may not be potent for the typhoid bacillus causing infection in a specific case. A further complication arises from the fact that typhoid and paratyphoid bacilli more frequently possess, or more readily develop, a resistance to the bacteriophage. In other words, most strains of *B. dysenteriæ* possess a natural susceptibility to all dysentery-active races of bacteriophage, while most, or, at least, many strains of *B. typhosus* (and this applies to the paratyphoids as well) possess a resistance, either natural or acquired, to bacteriophage. From the particular point of view of applying bacteriophage therapy, it may also be significant that in infection the typhoid bacillus does not remain confined to the intestinal tract. The fact that typhoid bacilli not infrequently, perhaps uniformly, invade the gall-bladder is of importance, for, as has been stated above, bile is definitely inhibitory to processes of bacteriophagia.

In view of all of these difficulties, and perhaps for other reasons also, bacteriophage therapy of typhoid infection has proved, in the main, distinctly disappointing, and yet in some isolated cases the treatment has yielded highly satisfactory results.

The details of the treatment as developed by different investigators have varied very widely, but despite all variations with regard to dosage and mode of administration, the results correspond closely. Either bacteriophage is promptly effective or it appears to exert no influence whatsoever. Where beneficial results have followed the administration of bacteriophage, the outstanding characteristic of the reaction has been the prompt fall in the temperature of the patient. This fall in temperature usually occurs within twenty-four hours of the time of injection, and as a rule from that time on the temperature remains within normal limits. The effect upon the presence of typhoid bacilli in the stool is less striking. In general, it seems that the treatment offers a greater possibility of being effective and, if effective, induces a more rapid and vigorous response in those cases with negative blood cultures. In connection with the influence of positive or negative blood cultures upon the effect of bacteriophage

therapy in typhoid and paratyphoid infections, the behavior of bacteriophage during the course of natural infection is not without interest, since in many cases it has been shown that during the later stages of the disease and particularly during convalescence, bacteriophage is to be found in the blood stream and the failure of many blood cultures to yield growth may reasonably be ascribed to bacteriophagic action. These facts suggest that the therapeutic administration of bacteriophage merely institutes, or supplements, those natural processes which favor spontaneous recovery.

Frequently, cases presenting positive stool and urine cultures become bacteriologically negative within the first twenty-four hours after the initial treatment, and as a rule such cultures remain negative, although cases have been reported in which, after a period of negative examinations, the stool cultures again became positive. Other cases have shown that the elimination of typhoid bacilli from the stools does not necessarily prevent a subsequent typhoid infection of the urinary tract.

In a number of instances attempts have been made to apply bacteriophage in the treatment of carriers, both of typhoid and paratyphoid bacilli. The evidence thus far indicates that nothing is to be expected in this direction, for almost without exception the strains encountered in carriers are of the resistant type.

The mode of administration most extensively employed in the treatment of typhoid and paratyphoid fevers has been a combined subcutaneous injection and oral administration.

For the injections, the quantity has ranged from 0.5 to 2 c.c., and the dosage given by mouth has varied from 2 to 15 c.c. In a few instances, the treatments have been repeated upon the two, or even upon four succeeding days, but judging from the recorded data, there is little reason to think that the amount administered is of extreme importance, or that repeated administrations offer very marked advantages.

Consideration of all of the reported studies warrants the opinion that under suitable conditions bacteriophage therapy may be applied advantageously in typhoid and paratyphoid fevers, but the method is far from being as successful in these infections as in bacillary dysentery. On the other hand, no one has yet suggested that treatment with bacteriophage is attended by any harmful reactions. Manifestly here, as in other infections, the parenteral administration of bacteriophage should not be continued over too long a period, for inasmuch as the bacteriophage is antigenic and leads to the development of antibacteriophagic principles, a treatment too intensive and too prolonged would but defeat its purpose, in so far as an immediate effect is concerned.

Although the question of bacteriophage as a prophylactic agent is not the subject at present under discussion, it may be permissible to state that the antigenic structure of the proteins of bacteria subjected to bacteriophagia is not lost through bacterial dissolution. A suspension of

typhoid bacilli which has undergone bacteriophagia and no longer con-
tains intact bacterial cells is still competent to function as an antigen, and
when administered as an immunizing agent leads to an antibody response,
more rapid in development, and essentially the same in character and
degree as that induced by the usual type of bacterial vaccines.

B. Coli Infections.—With the possible exception of bacillary dysentery,
no class of infections has received more attention from the standpoint of
bacteriophage therapy than those due to *B. coli*. Certainly more inves-
tigators have attempted to apply bacteriophage in the treatment of colon
bacillus infections of the various types than have approached the study
of any other disease, and here again, as in the case of typhoid fever, the
results have been extremely variable. Many have attained what they
consider phenomenal results, while others have recorded data decidedly
discouraging. The cause for such discrepancies is obvious, in part at
least, for colon bacilli are heterogenic to the highest degree. They exhibit
a very pronounced strain specificity as regards their behavior toward
bacteriophagia. Furthermore, like typhoid bacilli, susceptible organisms
readily become transformed into resistant forms and, consequently, when
this change takes place, whether it be induced by inappropriate or inade-
quate treatment or whether due to natural causes, bacteriophage therapy
offers little, if any, hope of success.

It may be pointed out that the intestinal tract is the normal habitat
within the body for both *B. coli* and bacteriophage, and in this location,
through repeated contact, bacilli of this type may readily develop a re-
sistance. Undoubtedly, many infectious processes are due to organisms
already resistant prior to invasion of the tissues. In view of these facts,
namely, that colon bacilli are heterogenic in nature and may readily
develop a bacteriophage resistance, it is necessary before bacteriophage
therapy of a colon bacillus infection is instituted to recover the infecting
organism in pure culture, and with it demonstrate susceptibility to bacterio-
phagia. In this connection it may be stated that thus far results with
"autobacteriophage" therapy, that is, the utilization of a race of bacterio-
phage derived from the patient under treatment, have been in no way
superior to those obtained when active, highly virulent "stock" or lab-
oratory races of bacteriophage are used. Thus it is not essential to prolong
the period of preliminary study with each patient, the only requisite
being that the organism recovered from the patient be tested for its
susceptibility to such races of bacteriophage as may be available. For
treatment, that race should be selected which has shown the highest degree
of potency for the bacterium in question. Unfortunately up to the present
time, a polyvirulent or multivirulent race of bacteriophage active for
colon bacilli has not been found, or at least the polyvirulence is not suffi-
ciently extended to guarantee without test that such a race will be effective
against a given strain of bacilli.

Infections of varied character due to *B. coli* have been subjected to therapy, cystitis and pyelitis in particular receiving the most attention. Methods of administration as well as dosage have varied greatly, with the result that at the present time there appears to be no accepted procedure. In general, in infections of this type, a combined method of administration has been employed. Subcutaneous injection with oral administration in pyelitis, and subcutaneous injection in conjunction with bladder instillation in cystitis.

Unlike dysentery and typhoid fever, in colon bacillus infections it would appear that repeated treatments may be definitely advantageous, particularly those treatments not involving a parenteral administration of the preparation.

In colon bacillus infections, as in other conditions, if treatment is to prove beneficial, improvement in the clinical state is prompt, and if evidence of an alleviation of the symptoms is not apparent after two treatments given with a twenty-four hour interval, it is generally useless to prolong the therapy. As a rule, an interval not greater than forty-eight hours should be allowed to elapse between treatments. Either the bacteriophage promptly institutes the phenomenon of bacteriophagia together with correlative phenomena of benefit to the host, or it has no influence at all, unless, perhaps, it serves to intensify the state of resistance possessed by the bacteria. Avoidance of a protracted series of subcutaneous injections would seem to be obligatory, since no possible immediate advantage could accrue to the patient through the elaboration of antibacteriophagic antibodies. Naturally this antigenic attribute is of moment only when bacteriophage is given parenterally. Repeated oral administrations or intravesicular instillations are inert in this connection.

In the many cases reported, the results have always been clear-cut, either improvement, both clinical and bacteriological, becoming apparent within a short time, a few hours to five days, or no change whatever being observed. Judging from the results recorded it would seem that the combined injection-ingestion or injection-instillation method had proved to be most effective. Usually, 2 c.c. of bacteriophage is injected subcutaneously and from 10 to 20 c.c. of bacteriophage is ingested, or from 10 to 20 c.c. of bacteriophage, usually diluted 1:10 with saline, is instilled into the bladder. To the injections, a slight local reaction may develop, but in the majority of instances this reaction is lacking or is insignificant.

Following the instillation into the bladder, no disturbing symptoms have been reported, and careful studies made in a few instances have shown that not only do the colon bacilli quickly diminish in numbers but other evidences of inflammation tend to disappear. Naturally, results of this type can be anticipated only in those instances where the infecting organism is susceptible to the bacteriophage employed, but it is of interest to note that in many cases a very definite improvement in the clinical

condition has been observed despite the fact that colon bacilli have persisted in the bladder. This suggests, and other observations both clinical and experimental are confirmatory, that infections induced by resistant organisms are less likely to be of the acute type. In other words, the acquisition of resistance on the part of the bacterium is correlated with a decrease in virulence. If this is true, it affords an explanation of the commonly observed fact that bacteriophage therapy is far more effective in the treatment of acute colon bacillus infections than in chronic conditions.

Some hundreds of case reports are now a matter of record, and an impartial consideration can but lead to the impression that as yet some of the more important determining factors governing colon bacillus infections remain unknown, and until these are discovered the remarkably satisfactory results of bacteriophage therapy in some cases, and the complete ineffectiveness of the treatment in others cannot be explained. But, as in typhoid and paratyphoid infections, the treatment is unattended by harmful results even though it be without benefit. For this reason, in some institutions the administration of bacteriophage to *B. coli* infections has become a matter of routine.

Vibrio Choleræ.—Unless it be in bacillary dysentery, the results of bacteriophage therapy have in no case been so phenomenal as in Asiatic cholera. Possibly it may be somewhat premature to attempt a final evaluation of this method of therapy in this disease, but in so far as the work has gone the results obtained are extremely satisfactory. Incidentally it may be said that in connection with cholera most striking results have also been obtained with regard to the prevention and control of epidemic infections. If the results thus far obtained are borne out by subsequent studies, it would seem that in bacteriophage an agent is at hand which may serve in limiting and controlling the spread of at least some of the epidemic infectious diseases.

In the treatment of cholera the bacteriophage is applied by oral administration. An initial dose of 2 c.c. of bacteriophage, diluted in 10 c.c. of water, is given the patient, and during the two or three hours following this treatment an additional 4 c.c. of bacteriophage diluted in from 40 to 50 c.c. of water is ingested. This latter quantity is taken gradually, a spoonful at a time, until the entire amount has been ingested. Very frequently following this treatment a definite improvement in the clinical condition of the patient will become manifest within a period of twenty-four hours. In these cases further treatment is not indicated. Other patients, somewhat more seriously ill, may fail to show definite improvement and in these a second treatment on the second day is given, again administering 5 or 6 c.c. of bacteriophage. Following the treatment, clinical improvement, in case it is ever to occur, manifests itself abruptly and is evidenced by a change in the character of the stools as well as in the

general condition of the patient. As a rule the vibriones disappear from the stools.

In the relatively small group of unselected cases (70) so treated, the mortality was 8.5 per cent, while in the control group of cases occurring in the same district and at the same time, including both cases which were untreated and those treated by other methods, the mortality reached 60 per cent.

No less striking have been the results attending efforts to prevent the spread of cholera throughout local areas, and the measures taken to bring about a termination of epidemics. In several villages in India, where cholera was present in epidemic form, the development of new cases of the disease ceased very abruptly following the introduction of cholera bacteriophage into the wells furnishing the water supply.

Thus, while in this disease the studies thus far made have not been sufficiently extensive to permit of a final decision as to the value of bacteriophage as either a therapeutic or prophylactic agent, the very striking effects observed are surely encouraging and justify further study.

INFECTIONS DUE TO ORGANISMS OF THE PYOGENIC GROUP

From its natural, normal location within the body and its general behavior, it might readily be conceived that bacteriophage should exert a marked influence upon infections confined wholly or in part to the enteric tract. It is not as obvious that bacteriophage should likewise play a rôle in infectious processes which localize outside of the enteric tract; more specifically, in those due to organisms of the pyogenic group. Nevertheless, even though the mechanism of its action is in many respects obscure, bacteriophage most assuredly plays some part in the processes of spontaneous recovery from pyogenic infection, and under suitable circumstances it can unquestionably be used to advantage in therapy. Bacteriophage has been employed widely as a therapeutic agent in infections due to the staphylococci, and to a lesser extent in those associated with streptococci.

Staphylococcus Infections.—Staphylococci belong to that type of organisms spoken of as heterogenic as regards bacteriophagia, but with these cocci is to be found a situation differing somewhat from that encountered in the other species which are heterogenic. For staphylococci, a polyvirulent bacteriophage has been found and, although individual susceptible strains may manifest a specificity as regards other races of bacteriophage, with respect to this particular race, all susceptible strains appear to behave in the same fashion. For this reason this particular race, Race h, of Gratia, is the one most widely employed in therapy, and with it the results obtained appear to be as satisfactory as when races exhibiting a more strict strain specificity are used.

Various types of stapyhlococcus infection have been subjected to bacteriophage therapy, the mode of application and the duration of treatment varying somewhat with the infection under consideration. Probably more work has been done in connection with furunculosis than any other type of staphylococcus infection, and here the results have been highly satisfactory. Apparently in acute infectious processes due to staphylococci the organisms are almost invariably of the susceptible variety. Chronic processes frequently contain organisms which are resistant. It would seem that the tendency for staphylococci to develop an acquired resistance spontaneously is less outspoken than is the case with some members of the enteric group of bacilli.

In the treatment of furunculosis, the bacteriophage is administered solely by subcutaneous injection, local superficial applications appearing to contribute no added benefit. Usually, two injections are given with an interval of from twenty-four to forty-eight hours. The quantity injected has varied from 0.5 c.c. to 3 c.c., but two doses of 2 c.c. each appear to be as satisfactory as any method of treatment.

The point of inoculation seems to be a matter of no particular consequence, since the results attending injections in the immediate vicinity of the affected area have not, as a rule, been superior to those where the material was injected in some more remote region. In the opinion of those who have applied the treatment most extensively, not only has it definitely accelerated the disappearance of the lesions, but in many instances it seems to have also influenced the recurrence of the infection.

In the treatment of local abscesses involving the deeper tissues, a similar method of treatment has been followed with success. In some instances and according to some observers, somewhat better results are to be obtained when the injections are given in the immediate vicinity of the abscess or, indeed, into the abscess itself. This latter procedure is, however, extremely painful and it is doubtful if the assumed added advantage makes such a method worth while.

Other workers advocate combining subcutaneous injections of bacteriophage with the local application of moist dressings. In this latter instance, the dressing is saturated with the same bacteriophage preparation as that administered by injection. In the treatment of infected wounds in which a staphylococcus is involved, a similar mode of treatment is followed. Here again subcutaneous injections appear to be beneficial but should not be continued over too long a period. The use of dressings moistened with bacteriophage or the direct introduction of bacteriophage solution into the wound may be continued as long as is necessary. Apparently such local treatment aids materially in removing the offending organisms from the infected area, and in this way facilitates recovery.

Bacteriophage therapy has been applied to otitis. Here, according to those who have used the method, local applications are indispensable and

can be most advantageously used in combination with subcutaneous injections. Sinus infections have been treated in the same way, as have also localized infections of the tonsils. Apparently in some instances the local application of staphylococcus bacteriophage together with subcutaneous injections have hastened recovery in cases of osteomyelitis, and in a few instances intravenous injections have been given in cases of blood stream invasion with staphylococci. A number of authors have reported upon the use of bacteriophage in the treatment of sycosis, the method most highly recommended being the somewhat painstaking procedure of inoculating bacteriophage in minimal quantities into each pustule as it develops.

Staphylococcus infections of the bladder and kidney are treated in the same way as are colon bacillus infections of these organs. In general it would appear that the results of treatment with staphylococcus bacteriophage are somewhat more favorable than the treatment of colon bacillus infections, although the rapidity with which improvement becomes manifest appears to be somewhat delayed.

In the case of furunculosis and localized abscesses, if improvement is to follow the treatment, some evidences of the changed condition usually become apparent within two to four days. In the case of infected wounds the improvement is not manifest as promptly. Very frequently the administration of bacteriophage is followed by an increased purulent discharge from the local lesion, but this quickly subsides and recovery follows.

Staphylococcus bacteriophage has also been employed in the treatment of leukorrhea with results that are distinctly encouraging. For this purpose, the polyvalent staphylococcus bacteriophage has been employed, applications being made by introducing, directly into the vagina, tampons impregnated with bacteriophage filtrate. This local treatment was repeated at from three- to five-day intervals upon two or three occasions, with the result that the staphylococci of the vaginal flora were definitely reduced in number and the clinical evidences of inflammatory reaction and cellular response disappeared. Healing was markedly accelerated.

It would seem that staphylococcus bacteriophage is somewhat more toxic than are most other bacteriophage preparations. As a rule, no general reaction follows the administration, but very frequently a local reaction of minor significance occurs at the point of inoculation and in some instances focal reactions have also been elicited.

In view of the great diversity of the infectious conditions referable to staphylococci which have successfully, in some cases, been treated with bacteriophage, it is obvious that pyogenic infection offers abundant opportunity for ascertaining not only the limitations of the method but the mode of action of bacteriophage.

Streptococcus Infections.—As compared with staphylococcus infections the use of bacteriophage in streptococcus infections has been extremely limited, and the results thus far obtained have been definitely less encour-

aging. For this there seem to be two obvious reasons. First, study of streptococcal infections indicates that resistant strains of streptococci are much more frequently encountered than are susceptible strains. In the second place, no one has yet succeeded in discovering a streptococcus bacteriophage possessing polyvirulent attributes. Streptococci, like staphylococci, represent an heterogenic species.

In a few instances, particularly cases of empyema and blood stream infection due to streptococcus, beneficial results have been obtained. In empyema, the bacteriophage is introduced directly into the infected area, relatively large quantities, from 25 to 30 c.c., being injected, the treatment being repeated on alternate days or on every third day until three treatments have been given. In cases where the streptococcus involved proved to be susceptible to the bacteriophage used, beneficial effects were noted.

In septicemia, injections of bacteriophage have been given intravenously; quantities of 1 c.c. being employed. In some instances within a few hours of the time of injection, a distinct fall in temperature has been observed, but usually it has been considered necessary to repeat the injection upon the following day. Under some circumstances, at least, this treatment has rendered the blood-cultures sterile. Cure has been effected only in those instances where the organism could be shown to be susceptible to bacteriophagia. Of the many cases of endocarditis subjected to bacteriophage treatment, none have responded to the therapy, and in every instance the organism involved has been shown to be resistant.

In considering the very limited success attending bacteriophage therapy in streptococcal infection as compared with the relatively much wider favorable experience in staphylococcus infections, it is impossible to avoid speculation as to how much of the effectiveness of bacteriophage is to be referred to the lytic phenomenon of bacteriophagia and what part is due to the outspoken activity of bacteriophage in stimulating phagocytic phenomena.

Gonococcal Infections.—But little work has been done in connection with the treatment of gonococcal infections with bacteriophage and there is no conclusive evidence at the present time that such treatment offers any material advantages. In the single contribution thus far made, the treatment with so-called "gonophage" appeared in some instances to hasten recovery, but the results were not outstanding. Indeed, a question may be raised as to whether the preparation "gonophage" corresponds in all respects to what is commonly regarded a typical bacteriophage. In the treatments with "gonophage" the material was administered by subcutaneous injection, the amounts given being extremely small (0.1 c.c. of a 1 : 1,000 dilution). At most, the results were inconclusive.

B. Pestis.—The number of cases of bubonic plague treated with pestis bacteriophage are also too few to warrant any definite conclusion

as to the general application of the procedure. In a few cases, however, the disease has been treated by injections of pestis bacteriophage directly into the infected bubo with results whose significance cannot be ignored. Into each enlarged gland 0.5 c.c. or 1 c.c. of bacteriophage was administered. Within twelve hours of the time of injection the temperature started to fall and within a few days the patients became convalescent. In these treatments the bacteriophage employed was that derived from the excreta of rats living in a plague endemic region.

If these observations can be substantiated, it may be that in bacteriophage we have for plague, as appears to be the case for cholera, an agent of the greatest importance from the point of view of both therapy and prophylaxis.

Other Infections.—Races of bacteriophage have been isolated which are active with several other bacterial species pathogenic for man, such as *B. diphtheriæ* and the pneumococcus. As yet, however, the use of these races as therapeutic agents has been too limited to merit discussion. Certainly no clear-cut beneficial results have been reported.

It is quite impossible to regard with indifference the results obtained with bacteriophage in the therapy of infectious diseases in many different localities and by many different investigators. Even those who hold very diverse views as to the nature of bacteriophage, its origin, and its mode of action find a point of agreement as to the distinct advantages which it offers in the treatment of certain infectious diseases. Unquestionably in bacillary dysentery, in cholera, in certain types of *B. coli* infection, and in some manifestations of staphylococcus infection the value of the method can no longer be questioned. Manifestly this treatment offers possibilities in the case of other infectious diseases, although as yet the conditions essential for its effectiveness have not been disclosed. Not only does this mode of therapy offer possibilities as to the more immediate alleviation of an infectious process, but it also appears that when administered under suitable conditions, the immunizing property of the bacteria dissolved in the bacteriophage preparation may be fully as efficient in leading to an organic immunity as are any of the vaccine preparations thus far devised.

Clearly in the light of our present knowledge bacteriophage therapy has certain limitations, these varying somewhat with the nature of the infectious organism involved. In the case of homogenic bacterial species such as *B. dysenteriæ* and *B. pestis,* the conditions governing the successful use of bacteriophage are less involved than in infections due to organisms appertaining to heterogenic species such as colon bacilli and staphylococci. But our lack of knowledge as to how many of these difficulties may be overcome cannot in any way negative the successes thus far attained.

The essential conditions for success are these:

1. The use of bacteriophage active for the organism causing the infection.

2. The use of a race of bacteriophage possessing a maximum virulence.

3. The use of bacteriophage in sufficient quantity to overcome the bacteria before their faculty of adaptation permits them to develop a resistance.

4. The limitation of bacteriophage therapy to those cases in which the invading bacterium is susceptible to bacteriophagia.

These principles must be borne in mind in further attempts to refine those methods now in use, and in efforts to adapt bacteriophage therapy to other infectious diseases.

CHAPTER IV

THE GENERAL CARE AND MANAGEMENT OF THE CANCER PATIENT

Douglas Quick

THE TERM "CANCER"

During the past few years a very considerable advance has been made toward better care of the cancer patient. Organized efforts looking toward cancer control through earlier recognition of the disease and clearer understanding of therapeutic procedures have brought the general problem into greater prominence. The use of the physical agents—radium and X-rays—has stimulated a different viewpoint and a new interest in therapy, and has given a great deal of encouragement in many directions.

The almost universal use of the term "cancer" is deplorable. It covers the entire group of malignant growths or neoplastic diseases—the largest group of closely allied diseases in the entire field of medicine. It carries with it in all instances the same mental picture or mental shock, depending on whether the recipient be casually or deeply interested in the particular patient in question. It at once places the basal-cell epithelioma or rodent ulcer of the skin in the same class with the deeply pigmented melanoma or the true osteogenic sarcoma. We have no term, fortunately, which places all infections of the respiratory tract on the same plane; which calls up the same mental picture for a rhinitis as for a pneumonia. Yet, such a term would be quite as reasonable as is the present conception and application of the term "cancer" to malignant diseases. We must come to think and speak of this large group of diseases as being closely allied in many respects, yet differing widely in many vital individual characteristics. We must apportion different values depending upon the advancement of our knowledge in the different general groups. We must, for the sake of family and patient, as well as for our own morale, submerge the term "cancer" and deal more accurately with malignant diseases as a vast group of allied diseases about some groups of which we are better informed and for which we can accomplish more by various combinations of treatment than in others. Fortunately, the advancement in the study of malignant diseases during the past ten years makes this approach to the general subject possible. Laboratory work, both clinical and experimental, has contributed a great deal to enlighten the public, and finally, treatment is on a more substantial basis.

CANCER CONTROL

The popular conception of "cancer control" to-day is that of an organized movement in which the laity in general as well as the medical profession is alike interested. The fundamental purpose is to disseminate as widely and generally as possible the latest and all knowledge relative to malignant diseases, thereby affording not only earlier recognition of the disease and more prompt and accurate treatment, but a stimulus to more intensive study as well. In moments of depression one cannot help wondering if this movement is not making pace faster with the public than with the profession. The need for more instruction in neoplastic diseases in our medical schools is urgent. The real cancer control of the future will depend very largely upon the equipment with which the medical student of to-day leaves our medical schools and teaching hospitals. The organized movements which have been put forth in many countries receive everywhere, and very deservedly, a whole-hearted support. The American Society for the Control of Cancer may very proudly claim to be the pioneer, and, with the British Empire Cancer Campaign operating in conjunction with the British Ministry of Health, leads the way in this great movement. The collection, dissemination, and stimulation in research of cancer data has led in many directions. Records of individual cases are being kept more accurately and in greater detail and consequently statistics of real value are coming to be available for the first time.

Various methods of treatment in different clinics are coming, in the same way, to be appraised and the results made more generally known. The study attendant upon this has led to the recognition of new subgroups of malignant diseases, clinical entities with certain specific features of which advantage may be taken from a therapeutic standpoint. The participation of the public in such a movement not only permits of a wider distribution of available knowledge, but encourages in the public a greater confidence in the measures sanctioned as being of value from the standpoint of treatment.

CANCER PREVENTION

This may very well be considered as a part of cancer control. It is true that we do not know the cause, or causes, of cancer—and more than probable that this generation will be denied the secret, if such there be. We are familiar, however, with many "contributory" causes: We recognize certain "precancerous" lesions. The removal or care of these is usually simple and while not as spectacular as the cure of an established malignant growth, is, in many respects, more important. The prevention of cancer by removal of a contributory exciting cause or removal of a tissue bed,

the seat of chronic inflammatory changes suitable for the development of
new growth, is more to be commended than the control of the lesion once
it is fully developed. It is by such measures that true cancer control will
become effective. It is only through a very substantial grasp of the entire
problem by the profession as a whole that such warning signs and pre-
ventive measures will be recognized and acted upon.

Chronic irritation of tissues is recognized as a definite contributory
factor in the development of malignant disease. In its simplest form it
may be noted on the skin surface, and in many instances either relieved
entirely or so reduced in severity that growth stimulus will be lacking.
The various senile changes in the skin are well recognized and are more
prone to malignant degeneration. In those exposed to the elements, these
changes may be more marked at an earlier period in life. Some individuals
have peculiarly sensitive skins which are prone to become irritated over
a period and remain so. This is particularly true with respect to sun and
wind burns. Occupational irritations of the skin may assume a great
variety of forms, and certain of these occupational dermatoses, some of
which ultimately become malignant, appear to be more specific than others,
notably, the chimney-sweep's cancer. Prolonged irritations may ultimately
provide a suitable soil for the development of new growth. Recognition
of the earlier changes in these conditions will naturally forestall the
ultimate and possibly more serious side. Certain drugs, notably arsenic,
which after prolonged administration produce a chronic dermatitis, in
certain instances are apt to be followed by the development of skin growths.

I doubt if in any of these conditions there is anything specific in the
sequence of events ending ultimately in the appearance of the neoplastic
process, usually rodent ulcer. It seems most probable that the changes in
the skin accompanying and resulting in the chronic dermatitis merely
furnish a suitable set of conditions for the subsequent development of
the neoplasm. The same is true of growths developing on the basis of old
X-ray and radium burns. The statement is often made that these agents
produce skin cancer after a time. Such is not the case. There is nothing
specific in the reaction to radiation in the skin, so far demonstrated, to
lend the least support to this idea. The atrophic changes furnish a suitable
set of conditions for the development of new growth. If the original skin
damage from radiation be relatively superficial and non-ulcerative in
character, basal cell carcinoma, similar to that found in connection with
other superficial irritants, is to be anticipated in a certain percentage of
cases. On the other hand, if the destructive process is deeper, influencing
more profoundly the entire thickness of the skin, squamous cell carcinoma
is usually the type of growth if a malignant process supervenes.

Contributory Factors in the Mouth.—Of all known contributory
factors, those incident to poor oral hygiene are most definite and most
pronounced. These may be briefly enumerated as rough and irregular teeth

presenting sharp corners and cavities in which food débris may be lodged; poorly placed fillings and neglected dentures, particularly fixed dentures which do not lend themselves well to cleansing. Ill-fitting dental plates should be particularly emphasized, since after a time they not only present surfaces about the teeth to irritate the membrane of the tongue and cheek but they are very apt to damage the alveolar borders without being noticed for some time. Over a period of years the contour of the bones of the face changes but the dentures remain the same shape. The wearing, therefore, of the same plates without readjustment for many years is a very frequent source of chronic irritation which ultimately develops into adult growth.

Dentists, as a group, are usually keen to recognize many of the early changes which may ultimately have a bearing on the development of new growths within the mouth, but they are often singularly negligent of the various factors which may be producing these early changes. Too many of them confine their activities to the direct repair of the teeth without taking sufficient cognizance of their patient's oral hygiene in general.

Excessive smoking undoubtedly plays a part as a contributory factor. The relative sensitivity of the mucous membrane varies to a considerable degree in different individuals. It is, therefore, smoking in excess of one's individual tolerance which does the damage. Within moderate limits, it apparently does no appreciable harm.

In connection with the tongue in particular, the persistence of heavy coating, which may be due either to accumulated débris or actual fungus growth, is capable of having far-reaching effects over a period of time. As a bacterial culture-medium it excels, and as such contributes toward the infection and reinfection of the lymphoid tissue about the pharyngeal ring.

Syphilitic manifestations within the mouth contribute, to a certain degree, toward the ultimate development of cancer—not because of any specific relationship between the two diseases but by furnishing a suitable tissue bed in which a new growth is prone to develop, just as in the case of the X-ray dermatitis on the skin. This is true in connection with either luetic leukoplakia or luetic glossitis, or both, since the latter is almost invariably accompanied by the former. True luetic luekoplakia is not uncommon, yet leukoplakia of luetic origin within the mouth accounts for only a small percentage of all intra-oral leukoplakias. It is fallacy to assume that all leukoplakia of the intra-oral mucosa is at once suggestive of luetic infection. Poor oral hygiene in general, points of irritation on neglected teeth or dentures, and excessive smoking account for the major portion of these changes. True luetic leukoplakia is usually more marked, involves the mucosa more deeply and is probably more prone to malignant change than leukoplakia incident to other causes.

The influence of oral sepsis as a contributory factor in the subsequent

development of cancer is probably not limited to the oral cavity. Its influence on the upper digestive tract particularly is probably far underestimated. All of these many simple factors attendant upon the proper daily and routine care of the mouth come constantly under the eye of the family physician and dentist. Unfortunately, in the routine course of events, they are too frequently overlooked or neglected. There is no doubt that a tremendous amount of intra-oral cancer could be avoided by proper attention to these simple details. It is the duty of the family physician and the dentist to take seriously and insist upon a proper recognition on the part of their patients of this phase of preventive medicine. It is not too much to say that with proper attention and coöperation intra-oral cancer could be almost completely avoided.

Breast.—Precancerous lesions and factors contributing toward subsequent development of new growths in the breast are less clearly defined than those just referred to. Certain outstanding features, however, are worthy of mention. It is only reasonable to look upon the frequent irritation of the areola and nipple as contributing something by way of changes which may ultimately terminate in Paget's disease. While the bleeding nipple has long been mentioned in textbooks as one of the cardinal signs of breast cancer, it is probably overdone on this score. On the other hand, it does call attention very frequently to the duct papilloma which, while in itself benign, does not always remain of the same structure—another example of the tissue in which change in structure is apt to take place as time goes on.

The subject of chronic mastitis is debatable and cannot here be discussed at length since we are concerned, for the moment, only with those changes which may ultimately contribute in some measure to the development of a malignant process. Since it produces mild yet persistent symptoms, and since it produces gross histological changes throughout the breast, it at least deserves the treatment which would be accorded a low-grade chronic inflammatory process elsewhere.

While the relationship between a single direct injury and the subsequent development of cancer is extremely debatable and undoubtedly rare, it is true in connection with the breast that an indirect hazard, at least, may be associated with such injuries as the scarring from the opening of abscesses and the careless introduction of hypodermoclysis needles. Definite instances of a relationship between the results of these injuries and the subsequent development of cancer occur from time to time. There is ample evidence, both experimental and clinical, at present to regard faulty drainage of breast secretion as another source of chronic inflammatory change which may contribute, in some degree at least, a suitable tissue bed for the ultimate development of growth. All forms of chronic breast inflammation, no matter what the source, should be regarded as dangerous to some extent at least and should be treated, in so far as practicable,

with the object of reducing or relieving this inflammation on account of its potential possibilities. If chronic inflammatory changes on a simple skin surface are capable of providing a suitable tissue bed in which a new growth may develop, it is only reasonable to assume that similar changes in a complex structure, such as the mammary gland, may be all the more dangerous.

Uterus.—Unusual uterine bleeding, and particularly any bleeding beyond the menopause, ought to be too well recognized as to its possible significance to call for comment, yet it is surprising how frequently it is ignored for a few weeks or even for a few months until malignant disease is well established, often beyond the possibility of cure. The conditions which so very frequently precede the cardinal evidence of new growth in this organ are, to a very large degree, overlooked entirely. Old lacerations of the cervix uteri, with the attendant tissue changes about these scars and with the inflammatory exudates from them irritating surrounding tissues, are usually ignored. This is merely another example of a condition, which, if corrected, would eliminate a considerable number of one of the commonest types of malignant disease.

Another source of chronic irritation and chronic inflammation which should be watched for and given proper treatment when recognized is the faulty drainage of secretion from the fundus uteri. Instances of the development of adenocarcinoma of the corpus uteri, associated with and incident upon this condition, are accumulating. Observations cn different races and classes of people whose habits differ point clearly to the fact that personal cleanliness in the habits of everyday life have considerable bearing on the relative percentages of carcinoma of the cervix in the different groups. The inference is self-evident.

Gastro-intestinal Tract.—In connection with the upper gastro-intestinal tract, that is, from the esophagus to the small bowel, we have little specific information as to definite contributory causes in the development of cancer which may be watched for on the part of the physician, or avoided. The varying degrees of sensitivity of the mucous membrane in different individuals makes the matter of irritation, from different types of food, a relative matter. It is doubtful if any practical, worth-while conclusions can be drawn. The suggestion that oral sepsis may be of greater importance in these organs than the character and temperature of the food taken is worthy of consideration and further investigation. In the colon and lower bowel certain anatomical abnormalities are of practical significance. Polypi and diverticula are recognized as potential points of irritation and inflammation. Malignant disease may subsequently develop in either. Unfortunately, both are apt to be multiple, so that it is usually impractical to remove all of the potential danger points. On the other hand, recognition of the condition plus careful routine watching will at once draw attention to any unusual change and thereby permit of proper

treatment of the suspicious area before unrecognized growth extends out of bounds.

Rectal bleeding should always be taken seriously. Whatever the source of bleeding may be, it should be corrected immediately. A diagnosis of hemorrhoids should never be concluded as such without eliminating the possibility of early new growth, and a diagnosis of hemorrhoids should never, under any circumstances, be made across the corner of an office desk.

In following the gastro-intestinal tract from the standpoint of cancer prevention, the clinician should be advised against placing too much reliance on negative X-ray findings in the lower bowel. The relative value of this diagnostic method is much greater in the upper tract than in the lower.

DIAGNOSIS

In the matter of cancer diagnosis, very little need be said. The apparent increase in cancer represents probably nothing more than an increase in the frequency of its recognition—in other words, more accurate diagnosis. Unfortunately, a large number of these diagnoses are made entirely too late. The facilities for diagnosis are, for the most part, very adequate. The unfortunate point is that the advantages of these facilities are too often neglected until the most favorable time for treatment has passed. It is on this point in diagnosis that stress should be laid most forcibly. If the clinician would regard cancer as a large group of closely allied diseases rather than as a single entity, a considerable advance would at once be made from the standpoint of diagnosis. The notion that anemia, cachexia, pain and foul discharges must be present before cancer is to be suspected is the greatest fallacy. At this stage a diagnosis of cancer is usually of value only to the department of vital statistics. Routine health examinations, if carefully and seriously done, will contribute tremendously toward the early diagnosis of many malignant growths. Unfortunately, most of these neoplastic processes are insidious in their onset and many may be practically symptomless. More examinations of the patient and less consultations, beyond a reasonable point, will advance and simplify the general problem of the care of the cancer patient.

With the present development of X-ray and laboratory aids to diagnosis, there is little excuse for overlooking most early new growths in a routine examination.

While a great deal has been said for and against the advisability of the taking of tissue from a questionable area for diagnosis, the practical fact remains that whenever in doubt, biopsy, where reasonably practical, will do far less harm than the leaving of a malignant growth to develop to the point where it establishes its own diagnosis. The resort to biopsy should, of course, always be determined upon reasonably. The piece of

tissue removed for section need not be large. Trauma of surrounding tissues should be avoided with the utmost care. The opening into normal tissues, either for access to the tumor-bearing area or by extending through the growth into normal tissues of the tumor bed, should be avoided wherever possible. If it is necessary, in obtaining tissue for histological examination, to gain access by surgical exposure, the wound should be closed very carefully by approximating the various layers of tissue incised separately, in order that subsequent fungation of tumor tissue may be avoided.

Within certain limits, external radiation as a therapeutic test may be of value in aiding confirmation of a tentative diagnosis where the tumor suspected is particularly radiosensitive. Lymphosarcoma furnishes probably the best example of this. On the other hand, one should not be deluded by placing too much dependence upon this type of verification. It is of value within very narrow limits only.

In the differential diagnosis of many tumors, particularly those presenting an ulcerating surface, tertiary syphilis must be considered. A positive Wassermann, however, must not be taken as conclusive that the lesion in question is undoubtedly luetic. Biopsy should also be resorted to if the clinical picture is at all questionable from a luetic standpoint. Antiluetic treatment should only be persisted in for a brief period in the absence of clinical improvement before reconsideration is given the diagnosis. A positive Wassermann, with or without a luetic history, does not preclude the possibility of other disease. Too frequently the possibility of cancer is ignored because of the positive blood reaction.

TREATMENT

The treatment of any malignant growth might well be considered under the following headings: Curative, palliative or psychological.

If, after giving due consideration to the type of growth and its degree of advancement, there seems to be a reasonable opportunity for its complete eradication, then the measures decided upon for the treatment of that particular case ought to be exerted to the limit, whatever those measures may be. On the other hand, if palliation only is possible, every consideration ought to be given the patient's comfort from day to day and no therapeutic measures resorted to which would unduly upset the patient when nothing definite may be anticipated in return.

Considering the entire field of malignant diseases, from the simple rodent ulcer, probably 95 per cent of which are curable, to the osteogenic sarcoma and the active melanoma, in which the expectancy of cure is very slight, the average of curability for the entire group of malignant diseases classed under the heading of cancer is probably about 20 per cent. This leaves a very large group in which palliative treatment, sooner or

later, comes to be the only resort. The degree of actual physical palliation, of course, varies with different types of the disease and is dependent upon many varied factors. In these cases, the manner in which they are handled from a psychological standpoint is most important and those who assume the responsibility of caring for these unfortunate people would do well to study most seriously the various psychological problems present in the individual case.

Specific Therapeutic Measures.—As far as the active and direct treatment of new growth is concerned, it is almost entirely a surgical problem. The only agents at our disposal at the present time for direct treatment are surgery, X-rays and radium. It is in the proper selection and application of these measures or in their various combinations that the chief advances have been made in the treatment of cancer during the last decade. Surgical technic has reached a high state of perfection. The technical procedures incident to the application of X-rays and radium are improving, yet the use of these physical agents is of such recent date that much more can be reasonably expected in the future than has been accomplished in the past. The value of these agents should not be appraised to-day on impressions or experiences gained from the manner in which they were employed a few years ago. It is in the development of proper usage of these physical agents, combined wherever advantageous with the benefits of conservative surgery, that most may be expected in the future treatment of cancer.

The physical agents should be regarded as just so much valuable additional equipment to add to the strictly orthodox surgical equipment which the surgical experiences of the past have brought to such a high state of perfection. It is no longer necessary to attempt an operative procedure on the inoperable case, simply because some effort at relief must be made. Furthermore, in the otherwise technically operable case, radiation in some of its various forms is very likely to be of assistance, either by way of rendering the surgical procedure safer or by limiting the necessity for some of the spectacular, yet extensive, operative procedures which have been attempted as heroic efforts toward controlling certain of the more malignant or more advanced types of disease. In other words, through the assistance of radiation, the character of present day cancer surgery has been very decidedly altered. Some of the most extensive operative surgical procedures have been entirely replaced by the physical agents. Of this, carcinoma of the cervix furnishes probably the most outstanding example. On the other hand, carcinoma of the fundus uteri remains a problem for operative surgery. The disease is of a different type both histologically and anatomically, and, as such, lends itself much better in the present state of our knowledge and advancement in therapy to surgical removal than to treatment by radiation. However, if the disease be advanced to such extent that complete surgical removal is not assured or, if for any

reason, the general physical condition of the patient does not warrant an extensive operative procedure, the benefits to be derived from radiation are such that the surgical steps may well be replaced by the other methods. In some cases, preliminary irradiation, followed by surgical removal of the growth, affords the patient a better chance for ultimate cure than would be the case if the surgical procedure alone were carried out. This is well exemplified in cancer of the breast. It not infrequently happens that an operative surgical procedure is undertaken with the expectation of being able to do a complete removal of the tumor, only to find as the operation proceeds that this is impossible. Through the advantages to be gained by implantation of radium emanation, an otherwise unsuccessful operation may be turned into a successful procedure by resorting to implantation of radium emanation to care for that portion of the growth which cannot be safely or successfully extirpated. The implantation of radium emanation, as an extra safeguard, as the final step in an otherwise clean surgical dissection, is in certain instances dependent upon a general routine procedure, as in the treatment of operable metastatic epidermoid carcinoma in the neck and inguinal regions.

Certain of the surgically inoperable tumors may, in addition to heavy external irradiation, be handled best by following this external treatment by surgical exposure of the tumor for the purpose of accurate radium implantation throughout the tumor-bearing area. In this connection, many new surgical procedures for the purpose of exposure and approach to tumor-bearing areas must be devised to meet the requirements of the individual case. It becomes apparent, therefore, that while some of the older surgical measures have been replaced by radiation, other surgical procedures have had to be devised to meet the ever changing conditions, as our knowledge of the application and value of the physical agents progresses. In other words, the character of cancer surgery to-day has changed to such an extent that it may well be considered one of the special fields of general surgery.

There should be no confusion as to the relative place of X-rays and radium in the treatment of cancer. X-radiation may be employed only for external application and for the most part over large areas. From an economic standpoint there are several advantages to be considered and there is no limitation on the supply. Additional X-ray equipment is always available. Radium, on the other hand, lends itself best to application within body cavities, over localized surface areas, and, most important of all, for direct implantation within the tissues. There is some difference in the quality of radiation between the gamma rays of radium and the hardest X-rays obtainable with our present day equipment. However, this need not be given particular consideration here. It is true that if adequate quantities of the radiation from both sources are available for comparison, the gamma rays of radium are more effective and more efficient than the

best that can be produced through an X-ray tube at this time. The supply of radium, however, is limited and the advantages which it affords must, of necessity, be limited to a relatively few patients. X-radiation must be depended upon to furnish the major portion of the external radiation in routine work throughout the country at this time. A good dose of X-radiation is always better than a poor dose of radium radiation. The treatment of larger tumors, particularly at depth, or the treatment of large surface areas by external applications of radium should never be attempted unless a large radium supply is available.

Quite apart from the relative position which radiation may hold in the treatment of the various types and groups of malignant disease, it is a fact that the use of these physical agents has changed very considerably the outlook on cancer in general. Its use has stimulated a tremendous amount of histological study, without which reasonable and intelligent application of the physical agents would be impossible. Through this intensive study, new conceptions of the general problems of cancer have been gained, and several new types of the disease have been recognized as definite clinical entities.

It would be impossible, here, to go into a discussion of the effects of radiation on tumor tissue. It might be well, however, to point out that the beneficial effect of radiation from a therapeutic standpoint is not limited to its effect on the tumor tissue alone. It is quite possible that the effect on the surrounding normal tissues or, as it has been very aptly termed, the tumor bed, is quite as important as the direct effect upon the neoplasm itself. This has a very considerable bearing not only on the technical methods of irradiation, but also upon the manner in which irradiation is combined with operative surgical procedures. The problems incident to the proper combination of these various methods and their application in the individual case, call not only for special facilities, but for special training as well. The time has arrived when special institutions for the treatment of cancer are quite as necessary as have been found to be necessary in the past for the treatment of certain other special diseases. Where special institutions are not available the cancer service in the general hospital is the least that can be considered, consistent with the present needs of dealing adequately with the cancer problem. This is not meant to suggest that the cancer patient be inevitably taken away from the family physician, but rather that the special equipment and special training necessary to assist the latter in meeting the peculiar problems incident to the individual case be made accessible to the man who, after all, must carry a very considerable portion of the burden in connection with the treatment of any case of malignant disease.

Constitutional Measures.—The general medical care of a cancer patient is too often overlooked or, for the moment, forgotten under the stress of the immediate problem. Malignant disease may and does exist

in conjunction with many other grave medical conditions. This is particularly true since the so-called cancer age is also the period of life during which the system begins to show the effects of wear and tear in general. Cardiorenal disease, diabetes, and tuberculosis must be cared for just as carefully or more so in the presence of cancer as at any other time. No strenuous therapeutic procedure, operative or otherwise, for cancer should be undertaken without a careful, unbiased appraisal of the patient's general physical condition quite apart from the immediate problems incident to the malignant condition itself. Acute symptoms referable to the chest should not be assumed always to represent an inflammatory process and that only. It may indicate secondary involvement by metastatic malignant disease. The implantation of tumor emboli in the lungs is always a shock which may manifest itself by acute symptoms for a brief period and which might well pass unrecognized, as being of bacterial origin rather than associated directly with the growth. General medical supportive treatment should ever be kept in mind and carried on vigorously in conjunction with the specific treatment of the tumor-bearing area itself.

The opinions of the internists will naturally vary as to the relative values of various types of tonic medication but, whether it be the administration by mouth of stimulants to digestion, intramuscular medication with iron and arsenic or stimulation of body surfaces by means of the quartz lamp, all measures that will aid in the slightest to maintain the patient's general physical condition at the highest level should be resorted to.

There is another reason, and a very legitimate one, for the vigorous use of these aids with detailed attention given thereto. The cancer patient is hanging for support on every possible bit of encouragement. It may be that a great deal of the value to be derived from these various measures is a psychological one. It does not matter whether the benefit is physical or mental—the result obtained is justification for the means. This brings us to consideration of another phase of medical treatment which may be open to some question, yet one which I believe has its advantages if honestly employed.

Specific Medication.—Each year brings forth its group of cancer "cures," each supported by its own cancer quack. They all have something to show for their claims although the evidence is always, unfortunately, magnified to a very marked degree. An analysis of the many general medical "cures" advocated during the past several years suggests strongly an underlying foreign protein reaction as being common to nearly all of them. Our experience with the unusual effects sometimes obtained through the employment of foreign proteins by virtue of the peculiar systematic reactions which they excite, might lead to interesting speculation as to their value in certain cases of malignant disease.

There are instances in which the systematic reaction of the patient may

be stimulated to carry over, when resistance is practically at a standstill, through the intramuscular injection of ordinary milk protein. It affords, furthermore, in some of the more advanced cases where palliative relief and moral support only can be given, a reasonable means of carrying the patient along. This might be regarded in some quarters as dishonest practice. It is legitimate to maintain the patient's morale and hope by any such measures, providing the patient's family understands the exact situation and shares in the delusion, if such it be. This must not be interpreted as advising or advocating the intramuscular injection of foreign proteins as an established or approved form of cancer therapy. It is merely suggested as a possible means of definite aid in certain selected cases and as a legitimate means of aiding, in certain instances, the very trying ordeal of carrying through the last stages the otherwise hopeless case in whom, but for some such resort, the last days would be made very unhappy because treatment had been abandoned.

Antiluetic Treatment of the Cancer Case.—It has been stated at times that antiluetic treatment of the patient suffering from both syphilis and cancer is contra-indicated, if treatment by irradiation is employed for the malignant growth. This is incorrect. It is true that aggressive treatment by irradiation is a very severe strain on the constitution of any patient. It is likewise true that aggressive antiluetic treatment is a very considerable strain on certain organs. In moderation, on the other hand, it will be found to enhance rather than damage the response to irradiation. The error is often made of carrying on intensive antiluetic treatment first and following this by treatment of the neoplasm. It is much better to save all possible time by treating the malignant growth as promptly as recognized, supporting this by a moderate course of antiluetic treatment and, after the patient has recovered from the effects of treatment of the new growth, to complete the antiluetic treatment by proper measures consistent with the patient's physical ability to stand the strain. With many new growths, particularly those presenting an ulcerating surface, antiluetic treatment alone is very apt to show an initial improvement in the tumor-bearing area. This is due to reabsorption, under the stimulus of this treatment, of inflammatory exudates in the tumor bed, and is very apt to be misinterpreted as definite improvement in the growth itself. It will, perhaps, do no harm to emphasize again the possible misleading effects of a positive Wassermann reaction. The two diseases may very well coexist. It is always wise, if there is the least uncertainty from the clinical standpoint, to go beyond the positive Wassermann reaction and substantiate the diagnosis of granuloma or neoplasm by histological examination of tissue. The general impression that biopsy may be harmful is unfortunate. The damage incident to the taking of a small piece of tissue is negligible. The time saved in beginning adequate treatment is of inestimable value.

THE FAMILY PHYSICIAN

It is easy enough for the physician who devotes himself largely or entirely to the care of malignant diseases to criticize the family physician's errors, particularly in establishing the diagnosis and getting the treatment under way. Apart from the special knowledge which his greater experience ought to give him, the specialist has the added advantage of viewing the case in retrospect. It would be much better for the specialist to give more time in an effort to further the family physician's knowledge of the many and various problems associated with the large group of malignant diseases. After all, this is the responsibility of any physician who assumes to treat cancer as a special problem. The family physician, on the other hand, must be familiar in a general way with a great number of medical problems and cannot be expected to be intimately acquainted with the many detailed matters incident to new growths in particular. He is too often ignored in the handling of his cancer patient and too frequently is removed from his association. This is not only an injustice to the general practitioner, but reacts, in many instances, to the disadvantage of the patient. The family physician should be kept thoroughly advised throughout the period of active specific treatment of his patient. All general medical measures, in so far as possible, should be left to him, with proper suggestion and advice. In the first place, he is better acquainted with the patient and with the patient's family and is therefore in a better position to maintain the morale of both. His active participation in this capacity, in the care of the case, permits of his maintaining the proper relation and dignity which is the right of the general practitioner. If the specialist and the family physician keep each other thoroughly advised throughout the period of treatment of the malignant case, each will be able to accomplish his particular part of the work to better advantage and the patient and family will benefit accordingly.

PSYCHOLOGY OF THE CANCER PATIENT

It is difficult to decide just how much should be told the cancer sufferer about his actual condition. Determination of this rests upon many factors. The patient who is able to maintain his balance and with whom everything can be discussed frankly and fully at all times is by far the most satisfactory patient to treat. Unfortunately, patients of this type are rare. Usually the manner in which facts are presented to the patient is of greater importance than how much or how little is actually told them. It is usually, or at least frequently, possible to give the patient a fairly clear insight into his condition without bluntly and crudely stating the actual facts in so many words. With a little caution and care he may be left with a rather clear visualization of what the situation is so that he may prepare himself in various ways and fortify himself to meet the

situation without having his morale entirely shattered through severance of that last thread of hope to which all of these patients cling. By the exertion of a little tact after appraising the situation, one may give a very honest impression to the patient, without disturbing him mentally to the degree that a simple, blunt statement of facts would perhaps do, even in the case of the most stoical.

The term "cancer" should be avoided most carefully at all times. The impression it conveys and the mental picture it promptly brings up are always startling and frequently are most misleading. It is an unfortunate term which should be used as little as possible. The cancer patient is inherently an optimist, whether admittedly so or not. Unless his morale can be maintained, therapeutic measures are bound to fail.

Relations with the Family.—In dealing with the patient's family, on the other hand, the confidences should be frank at all times, and never more optimistic than the actual facts of the situation warrant. It is, of course, frequently and perhaps usually, necessary for the mental satisfaction of those concerned to discuss the patient's problem with several members of the family. It is best, however, whenever possible, to carry on one's relations as physician or surgeon in charge, only with the most responsible member of the family, letting him, or her as the case may be, relay the information to other members of the family and their immediate friends.

In dealing with the family, one must insist upon an appearance, at least, of cheerfulness and optimism, even in the face of adversity, for the sake of its influence on the patient's morale. Reasonable consultations should be welcomed at all times. One is never in a position to guarantee anything in the treatment of any case of malignant disease. Not only for the purpose of safeguarding one's own position in the responsibility assumed, but for the satisfaction of the family as well, consultation should be ample, bearing in mind that too many consultations are apt to confuse the issue and to create an atmosphere of both suspicion and apprehension on the part of the patient.

In dealing with the more advanced stages of the disease, where a limited degree of palliative treatment only can be resorted to, it becomes the duty of the physician in charge to safeguard the family against doing many things which they might ultimately regret. There is a very strong tendency at times, under such circumstances, to resort to various questionable measures, some of which may be none too honestly presented to them. We must remember that if we are unable to do the patients any good, we are charged with the responsibility of doing them no harm. Nothing is more deplorable than to take an advanced case of malignant disease from one consultant to another. Adequate nursing care under the general medical supervision of the physician saves the patient a tremendous amount of physical and mental strain.

PALLIATIVE TREATMENT

Palliative treatment may be variously defined. It may be regarded simply as those measures incident to carrying the patient along to the end. It would be better, however, to consider it as treatment actively and seriously carried out and tending toward the relief and control of symptoms in so far as possible, even while recognizing the inevitable termination of the case. Prolongation of life alone, by various measures, is rarely justifiable unless it is attended by a reasonable degree of relief from symptoms; foremost among these symptoms being pain and the unpleasantness of irritating discharges and foul odors. Fortunately, in connection with controlling ulcerating, discharging and bleeding surfaces, radiation may well be considered a blessing indeed to the cancer sufferer. While opinions may differ as to the relative values of radiation as a curative agent, there is little room for debate as to its value as a most efficient aid in the control of these symptoms. Throughout a period of palliative treatment, most careful attention to constitutional measures and specific therapy, as previously mentioned, should be given, not only on account of its actual value but because of its influence in maintaining the morale of the patient.

Transfusion.—In the treatment of malignant diseases in general, the indications for transfusion are rather clear-cut. As an aid in carrying many patients through serious operative procedures or in maintaining their strength throughout prolonged periods of radiation where ultimate control of the disease may be reasonably hoped for, the value of a transfusion cannot be overestimated and should be resorted to frequently and liberally. On the other hand, it is very questionable if such a measure should be employed simply to carry on and prolong a course of palliative treatment. There are, of course, exceptions which must be decided upon their individual merits, but as a general rule the value of transfusion in the latter instance is decidedly questionable.

Use of Drugs.—In the use of sedatives, the utmost of caution should always be exercised. The cancer case usually is of long duration and once started on opiates, it is difficult to withdraw or reduce the amount given. Pain, of course, must be relieved, but a very sharp distinction should be drawn between actual pain and that restlessness which may follow a period of pain during which opiates have been used for its relief. With many ulcerating lesions where pain is dependent more upon the pressure of inflammatory exudates round about the tumor-bearing area than upon the actual pressure of the tumor itself, vigorous cleansing measures will do a great deal to lessen the need for sedatives. Frequent and careful irrigations with warm, mild, antiseptic solutions are of inestimable value as substitutes of sedatives under such circumstances. The use of heat, especially moist heat, should be employed wherever possible. In fact, all

physical measures, such as hydrotherapy, phototherapy and chemotherapy should be used wherever possible to avoid drugs. The type of pain experienced in many malignant cases is relieved better by salicylates than by opiates, and it is almost invariably true that the combination of salicylates with codein is far more advantageous than the use of codein or morphin alone. If the medication in the beginning of any of these cases is started properly, there are few patients in whom $\frac{1}{2}$ grain of codein with 10 grains of aspirin will not give relief, even under adverse circumstances, for a period of several hours, and a proper management of such sedative medication will frequently suffice throughout the average case even though the disease itself is not being controlled.

Apart from the immediate period attendant upon a major surgical procedure, and frequently even then, morphin should be carefully avoided and employed only as a last resort for relief in the terminal stages of the disease. If one is extremely cautious in the beginning, there are very few of the terminal cases which require any appreciable amount of morphin. It is much better to increase very considerably the amount of codein given than to change to morphin. The depression and the degree of gastro-intestinal disturbance are less. As a rule, the various coal-tar products are not desirable as sedatives in the treatment of cancer. If the demand for sedative is because of pain, these various drugs usually do not relieve it. If the demand is on account of restlessness, it can be relieved by the other measures mentioned to better advantage.

There is a great temptation, at times, to use cocain regularly on painful surfaces. This is extremely dangerous because the amount of absorption, even over a short period of time, has a deleterious effect on the patient; and if the local benefit is to be maintained, the amount must be increased rather rapidly. It is best to avoid it by not initiating its use. Moist heat will very often accomplish much more satisfactorily that for which cocain is ordinarily employed.

CHAPTER V

VITAMINS

George R. Cowgill

GENERAL CONSIDERATIONS

For almost a hundred years it has been known that a diet consisting of a mixture of the proximate principles, protein, carbohydrate and fat, separated from the other substances with which they occur in natural foods, together with a supply of inorganic nutrients, will not meet the requirements of normal nutrition. All attempts to feed such mixtures successfully met with failure. The most significant suggestion as to the cause of failure was received from the work of Hopkins (1912), who showed that such a diet could be made adequate for growth of rats by the daily addition of an amount of milk too small to permit of its beneficial effect being due to the protein, carbohydrate or fat contained therein. These experiments suggested that milk contains some hitherto unrecognized substance or substances which must be present in the diet if proper nutrition is to be maintained. This work of Hopkins was soon followed by that of a great many investigators, notably Osborne and Mendel, Funk, McCollum, Holst and Frölich, Evans and Bishop, all of whom secured experimental evidence to support the thesis that in addition to the known essentials for nutrition, such as protein for example, there are others which are required in only relatively small amounts. These newly discovered substances have been variously labeled, perhaps the most common designations being "accessory dietary essentials," "accessory food substances," "food hormones" and "vitamins."

Certain diseases for a long time have been recognized as being related in some way to diet. Beriberi among the peoples of the Far East and scurvy among sailors on the high seas are in this category. Elucidation of this relationship has finally resulted in the acceptance by clinicians of the term *deficiency disease* as the name for any characteristic syndrome, the development of which is due to the too prolonged subsistence on a diet lacking one or more of these "vitamins."

The crucial test of the vitamin hypothesis rests on the following facts: (1) the pathological condition in question only occurs when the individual, man or animal, has subsisted for a considerable period on a deficient diet; (2) the abnormal condition is cured by the administration of a sufficient amount of some source of the appropriate vitamin; and (3) when the

organism is fed the deficient diet together with a daily small but adequate source of the vitamin, the pathological condition does *not* develop. These statements might be regarded as the vitamin postulates analogous to those formulated by Koch for the field of bacteriology. Any claim to the discovery of a new vitamin requires, before it can be allowed, the submission of positive evidence based on an experimental application of these postulates.

It is as a result of efforts made toward isolating one of these hitherto unrecognized essentials of nutrition that the word vitamin now figures so prominently in the literature. Funk, who had accepted the idea that beriberi is a deficiency disease and had used the beriberi-like condition occurring in pigeons, fed on polished rice, as a basis of study, made many attempts to isolate from rice polishings and yeast the curative principle that was so potent against this disease. Although he did not achieve this completely, Funk secured a material that was extremely effective in almost infinitesimal amounts. Because he believed his material to be of vital importance to living organisms, and because this product appeared to belong to the group of substances designated by the organic chemist as amins, Funk proposed to call this compound vitamine (vital amine).

Since Funk's introduction of this word students of nutrition have discovered the existence of other substances of a vitamine character. In order to distinguish them, pending the elucidation of their chemical nature, McCollum and Kennedy (1916) suggested that each be given a letter and that outstanding solubilities be used in constructing a classification. Discussions in this field then centered around fat-soluble A vitamine, water-soluble B vitamine, etc. Inasmuch as the use of a final "e" in such a word as vitamine is interpreted by organic chemists to mean that the exact chemical structure of the substance is known, whereas dropping this letter connotes the opposite, Drummond (1920) suggested that the word *vitamin* be used to designate the group and that the individual members of the group be given a letter. When the exact structure of a given vitamin molecule is finally worked out by chemists, a new name suggestive of that structure can be devised.

CLASSIFICATION

The outstanding facts concerning the vitamins are summarized in the following table. For a more detailed consideration of the individual topics the reader is referred to the monographs and papers listed at the end of the chapter.

VITAMIN B

Vitamin B was the first of the accessory dietary essentials to which the term vitamin was applied. Recent researches make it quite clear that what has hitherto been called vitamin B is a mixture of at least two

TABLE I—THE VITAMINS

Name	Physiological Importance	Distribution
VITAMIN A fat-soluble	1. Growth. 2. Cure and prevention of: xerophthalmia, nasal sinusitis, infections of salivary glands, lung and kidney, lithiasis. 3. Proper maintenance of estrual cycle and ovulation.	*Large* amounts in cod-liver oil, butter, spinach, egg yolk, tomatoes. *Moderate* amounts in orange juice. *Small* amounts in nuts, cereals, cabbage, celery. *Lacking* in yeast, "refined" foods as white flour, starch, sugar.
VITAMIN B water-soluble It is suggested that the term *vitamin B* be understood to mean the mixture of antineuritic and heat-stable factors as found in natural foods. Considered individually these factors might be called vitamins F and G.	B₁. Cure and prevention of beriberi: so-called *antineuritic* factor; probably the factor required to maintain appetite under certain conditions; may be related etiologically to characteristic cutaneous ulcers. Inactivated by high temperatures. B₂. Heat-stable, so-called "growth-promoting" factor required to supplement B₁ in promoting growth. May be identical with B₃. Pellagra-preventive factor. Heat-stable.	*Large* amounts in brewer's yeast, wheat embryo, tomatoes, spinach. *Moderate* amounts in milk (variable), liver, peanuts, orange juice. *Small* amounts in muscle, pecans, egg yolk. *Lacking* in "refined" foods as white meal flour, all fats and oils.
VITAMIN C water-soluble Very sensitive to oxidation.	Cure and prevention of scurvy.	*Large* amounts in orange juice, raw and canned tomatoes, raw cabbage, lettuce. *Moderate* amounts in grape fruit, sprouted grains, raw carrots. *Small* amounts in milk (variable). *Lacking* in yeast, unsprouted grains, "refined" foods as flour, all fats and oils.
VITAMIN D fat-soluble Probably identical with a substance formed from ergosterol by exposure to ultraviolet rays.	Organic factor curing and preventing rickets under certain conditions. A dietary substitute for exposure to sunlight or ultraviolet rays.	*Large* amount in cod-liver oil. *Moderate* amounts in butter and egg yolk.
VITAMIN E fat-soluble	Organic factor that cures and prevents the sterility that is characterized by resorption gestation.	*Large* amounts in wheat embryo, lettuce, cereals. *Moderate* amounts in muscle. *Small* amounts in butter, visceral organs. *Lacking* in cod-liver oil.

substances that supplement each other physiologically. In discussing this vitamin, therefore, each of these substances will be considered briefly.

Antineuritic Factor.—Reference has already been made to Funk's efforts toward the isolation from rice polishings and yeast of the substance

able to cure the beriberi-like symptoms developing in pigeons subsisting on polished rice, and his suggestion of the term vitamin as a name for this product. The phenomena occurring in such birds are so striking and have been confirmed by so many investigators that they merit some attention. In Figures 1 and 2 are shown one of Funk's pigeons as it appeared before and after treatment with the vitamin concentrate prepared from yeast.
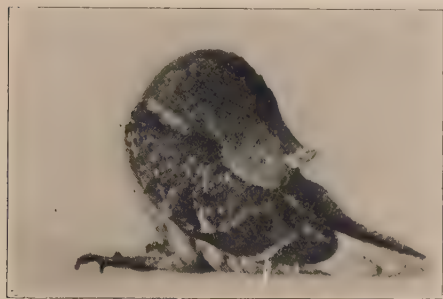
FIG. 1.—SPASTIC POLYNEURITIS IN PIGEON BEFORE TREATMENT. (Funk.)

FIG. 2.—SAME PIGEON AS IN FIG. 1, THREE HOURS AFTER TREATMENT WITH 4 MILLIGRAMS OF YEAST VITAMIN. (Funk.)

Numerous investigators have confirmed such observations, and have used pigeons extensively as subjects upon which to test many chemical fractions obtained in efforts to isolate the antineuritic material.

Other species of animals as well have been found to require this substance in order to prevent the appearance of nervous and muscular symptoms and paralysis, notably the rat, dog, cat and goat. The dog shown in Figures 3 and 4 was fed an artificial diet consisting of the protein commercial casein, cane sugar, butter, bone ash for roughage and a special salt mixture (Cowgill, 1921). At the end of about sixty days' subsistence on this ration the animal exhibited the condition depicted in Figure 3.

The administration of a small amount of tomato juice by stomach resulted after eighteen hours in the condition shown in Figure 4. The nervous and muscular manifestations of vitamin B deficiency had disappeared except for a peculiar "steppage" gait that characterized the dog for several days.

Further experiments have shown that intravenous injection of a suitable concentrated extract of the antineuritic material into such a dog may be followed by disappearance of the symptoms in as short a period as four hours. Such a result is quite comparable to that obtained on the pigeon. It should be emphasized that other dogs, fed precisely the same food as the animal shown in Figures 3 and 4, plus a small daily allowance of a vitamin concentrate, failed, over an observation period of approximately a *year and a half,* to develop any symptoms whatever.

FIG. 3.—SPASTIC PARALYSIS RESULTING FROM DIET DEFICIENT IN ANTINEURITIC VITAMIN B. (From Cowgill, *Am. J. Physiol.*, Balt.)

FIG. 4.—SAME DOG AS IN FIG. 3, EIGHTEEN HOURS LATER, SHOWING EFFECT OF ADMINISTERING NEUTRALIZED TOMATO JUICE.

After such treatment the animal was able to walk although with a characteristic spastic or "steppage" gait. After repeated treatments extending over four days, the spasticity of the leg muscles and the spastic gait almost entirely disappeared. (From Cowgill, *Am. J. Physiol.*, Balt.)

Water-soluble "Growth-promoting" Factor.—Information concerning the existence of this substance has come from investigators experimenting with various artificial rations on the young rat. Thus, Osborne and Mendel, in 1913, reported experimental evidence pointing quite definitely to the presence in milk of a water-soluble substance important for growth and adult nutrition and different from any of the known constituents of the diet. Other investigators, too numerous to mention individually, have contributed further evidence in support of this view and have attempted to isolate the substance. Many of the earlier studies on this topic have pointed to a close resemblance or identity of the growth-promoting factor and the antineuritic vitamin. This question of the possible identity of these two factors has had considerable debate. The more recent contributions toward a solution of this problem, however, indicate quite definitely that at least two substances are involved. It has been found that the antineuritic factor in yeast may be destroyed by high temperature; the yeast so treated, however, still containing a substance that supplements the antineuritic vitamin in allowing growth. Furthermore, careful studies of the efficacy of various plant and animal sources of vitamin B (1) in preventing and curing nervous symptoms and (2) in supporting growth, show such sources to differ considerably. This could hardly be the case if both of these physiological reactions were related to the same substance. Growth requires the presence in appropriate amounts of both the heat labile antineuritic factor and the heat-stable, so-called "growth-promoting," substance. In view of this fact, designation of the latter entity as "growth-promoting," as has been done so often in the literature, is inaccurate and undesirable (see Smith, 1928).

Pellagra-preventive Factor.—Especially interesting in this connection are the findings of Goldberger and his associates who have been studying pellagra (1926). These investigators have found that autoclaved yeast contains what they choose to call a *pellagra-preventive* substance. Students of vitamins are thus faced with the question: Is the so-called "growth-promoting" fraction of vitamin B identical with the pellagra-preventive substance?

In the light of these developments it has been suggested (Sherman, 1926) that (1) the term vitamin B be understood to mean the mixture of antineuritic and heat-stable fractions as they occur in natural foods and are required to allow growth; (2) that vitamin F be used to designate the antineuritic factor; and (3) that vitamin G be used for the heat stable pellagra-preventive substance. Curiously enough these are the initial letters of the discoverers, Funk and Goldberger respectively. If future research indicates that the pellagra-preventive factor is different from the so-called "growth-promoting" fraction, the letter H can be used for the latter component.

Vitamin B Deficiency and the Urge to Eat

The Phenomena.—In much of the earlier work dealing with vitamin B deficiency considerable loss of body weight by the experimental animals was noticed. Too often, however, the investigators made no observations of food intake. Osborne and Mendel (1917), in discussing their experiments where dried yeast was used as the sole source of water-soluble vitamins in diets for young rats, expressed the opinion that this vitamin favorably influenced metabolism, improving the general condition of the animal and thus indirectly promoted the urge to eat or appetite. In later experiments it was demonstrated that an animal's desire for vitamin B-free food can be improved by feeding the vitamin separately.

Karr (1920), following Mendel's suggestion, was able to show with the dog that absence of vitamin B from the diet and restriction of the animal to that diet, soon results in an erratic behavior with respect to food intake, a condition that is readily corrected by administration of suitable amounts of the missing vitamin. These studies were extended by Cowgill (1921), who was able to establish quite clearly a definite relation between the presence of vitamin B in the ration and maintenance of the urge to eat this food. In Figure 5 are presented graphically the data from one of his dogs. It will be noticed that periods, during which the animal ingested the food offered, were characterized by maintenance of body weight, whereas those periods, in which the urge to eat was lost, were marked by a definite decline in body weight. These observations were confirmed on many animals.

Control experiments using such a material as commercial beef extract, which does not contain vitamin B but which has often been used by clinicians endeavoring to promote appetite, have yielded negative results. In one case a small dog received during a period of about two weeks the extract of as much as 40 pounds of meat without restoration of the urge to eat; a prompt and positive effect was obtained, however, when a small amount of a yeast extract was given.

In certain experiments a yeast vitamin concentrate was injected intravenously and the appetite thereby restored. Such experiments emphasize still more the unique and specific relation that this accessory dietary essential bears to the urge to eat.

Further investigation of this phenomenon has brought to light many interesting facts. It has been possible to show that a definite relationship exists between the amount of a given source of vitamin B required to preserve the animal's appetite for the artificial ration over long periods—several months to a year and a half—and the size of the animal expressed in terms of body weight. In other words, the amount of vitamin administered is important. It has proved possible to secure quantitative data as well with other species, such as pigeons and rats. The importance of such

investigations will be realized more fully when it is appreciated that
knowledge of a human being's requirement for this vitamin can only be
gained indirectly. Should quantitative studies on several species reveal
some underlying law governing an organism's requirement, then vitamin
B therapy for human beings will be entitled to be placed on a sound
quantitative and scientific basis.
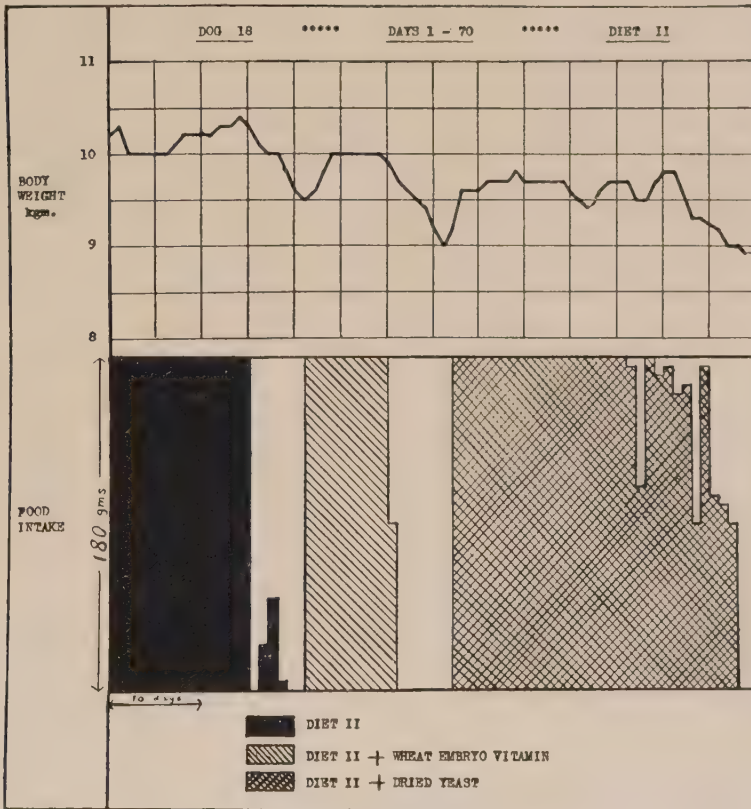
FIG. 5.—FOOD INTAKE AS INFLUENCED BY VITAMIN B. (From Cowgill,
Am. J. Physiol., Balt.)

The basal diet (II) lacks Vitamin B. The administration of an extract of wheat
embryo—Vitamin B—restored the urge to eat the basal ration. Likewise anorexia was
corrected by a single large dose of dried yeast. It will be noticed that the body weight
changes were determined largely by the food intake.

Clinical Considerations.—The problem of combating anorexia is fre-
quently quite baffling. It is not logical to conclude from the demonstrated
relationship between loss of appetite and vitamin B that a lack of this
vitamin is always the cause of the anorexia. Nevertheless, the rôle which
this dietary essential plays in maintaining the desire to eat should be
recognized, and lack of this vitamin should be eliminated as a cause of
the anorexia in question.

Many marasmic infants, undernourished and apparently unable to thrive on the food offered, have shown remarkable improvement in their general condition and a resumption of growth as a result of the addition to their food of liberal amounts of materials rich in vitamin B (Eddy and Roper, 1917; Byfield and Daniels, 1920; also further unpublished observations of Eddy). Eddy remarks: "While it is difficult in such cases to conclude absolutely that the appetite has been affected, the behavior of the child after receiving the vitamin, particularly the new interest it displays in the bottle and in feeding, suggests that the therapeutic agent, namely vitamin B, has acted somehow to restore the desire to eat."

Newburgh has reported to the writer a case of a young woman, defective mentally, who exhibited such a marked anorexia that her daily intake of food over a considerable period was extremely small, and expressed in energy was approximately 500 calories per day. Administration of liberal amounts of a good source of vitamin B was followed by a restoration of appetite, the patient voluntarily increasing her daily energy intake to about 2000 calories.

The writer has heard it said that little attention need be paid to vitamin B by the clinician, because it has not been demonstrated that the average American dietary is deficient with respect to this accessory factor. In the light of the cases just described the wiser policy for the clinician to follow would seem to be to make certain that all patients are receiving really liberal amounts of this vitamin.

Gastric Motility in Vitamin B Deficiency

Carlson and his associates have gathered together considerable evidence for the idea that contractions of the empty stomach constitute the physiological basis of the hunger pangs. Reasoning that cessation of such contractions might be the cause of the loss of appetite that occurs during vitamin B deficiency, Cowgill and collaborators (1926) recorded the gastric contractions in dogs subsisting on diets lacking this accessory factor. It was found that, as a rule, no very pronounced changes in gastric motility occur in the early stages of the deficiency, when the only sign of the deficiency otherwise is a loss of appetite. In advanced cases of the deficiency gastric atony usually prevails. It cannot be said, therefore, that the loss of appetite characteristic of vitamin B lack is due to a disappearance of the so-called hunger contractions. On the other hand, the results obtained certainly showed that administration of liberal amounts of vitamin B promotes the physiologic well-being of the alimentary tract.

Vitamin B in Relation to Lactation

Infantile beriberi is of frequent occurrence among people of the Far East. Chamberlain and Vedder, in their studies of beriberi in the Philip-

pine Islands, succeeded in showing that infantile beriberi can be cured by the administration of an extract of rice polishings while permitting the infants to be nursed by their mothers. As Vedder remarks: "This evidence that infantile beriberi can be cured by the same extract which cures fowls and cases of adult beriberi is not only additional evidence of the strongest kind that infantile beriberi, adult beriberi and polyneuritis gallinarum are all the same disease, but it definitely disposed of the theory that infantile beriberi is caused by an intoxication, since it is most irrational to believe that such an extract of rice polishings could cure a child in a few days, while it was still receiving the toxin which had originally produced the condition."

A most important paper dealing with this subject was contributed by Andrews (1912), in which he for the first time correlated the clinical study of the infant and mother suffering from beriberi with the autopsy findings and with analyses of the mother's milk, and also succeeded in producing experimental beriberi in puppies that were allowed to suckle upon mothers whose children had just died of beriberi.

These clinical findings have received excellent support from studies in rats on the relation of diet to lactation. Sure (1928) especially has shown that the beriberi-like symptoms occurring in rat sucklings may be obviated by merely increasing the amount of vitamin B in the food given the mother rat. Sure has also been able to obtain quantitative data of special interest. Not only has he found that direct administration of a vitamin B concentrate to the baby rat brings about a cure, but that in order to nurse a litter successfully the mother rat needs from four to five times as much vitamin B as she requires ordinarily for the proper physiological maintenance of her own economy. This investigator estimates that approximately 60 per cent of the vitamin B ingested by a lactating rat is "wasted" in the metabolic transfer through the mammary gland into the milk.

Macy and her associates (1927) studied the vitamin B content of human milk and found it to be inferior to cow's milk in this respect, and hardly to be regarded as an excellent source of this important dietary essential. In the light of the quantitative studies of vitamin B requirement in different species made by Cowgill and collaborators (1927), it cannot be said dogmatically that the human milk studied by Macy and her associates was really deficient in vitamin B, because the exact requirement of the human infant for this substance cannot be stated. However, in view of the studies of infantile beriberi mentioned above and the relation of vitamin B in the mother's diet to the well-being of the suckling, one is justified in emphasizing the importance of guarding the diet of the mother with respect to this accessory factor and feeding liberal amounts of this vitamin. Also, there is considerable warrant for the administration of liberal amounts of vitamin B to bottle-fed babies, especially in view of

the variable and usually low content of this substance in human and cow's milk.

Cutaneous Manifestations of Vitamin B Deficiency

Gerstenberger (1923) observed thirteen cases of *herpes stomatitis* and *herpes labialis* which yielded in remarkable fashion to the administration of yeast vitamin powder (Harris), a concentrated form of vitamin B. The absence from this preparation of the other vitamins would seem to point toward the B factor as the curative agent.

More recently, Cowgill, Stucky and Rose (1928) have observed the formation of ulcers on various bony prominences, particularly on the limbs of many of their dogs subsisting on diets adequate except for vitamin B. In Figures 6 and 7 are shown photographs of such lesions in the preulcerative and late stages.

The remarkable symmetry in distribution of these ulcers and the fact that they were produced in animals fed upon carefully controlled diets are points worthy of note. In some of their animals placed on the deficient diet twice, the "complete" ration being fed in the intervening period, these lesions developed twice, *associated each time with the defective diet, and disappearing when vitamin B was administered*. The absence of the cardinal signs of inflammation in these ulcers further indicates their malnutritional origin.
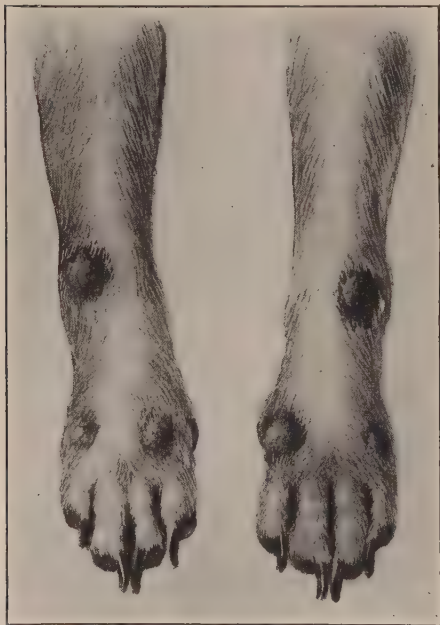
FIG. 6.—PREULCERATIVE STAGE OF CUTANEOUS LESIONS APPEARING IN DOG ON A DIET ADEQUATE EXCEPT IN VITAMIN B. (From Cowgill, Stucky and Rose, *Arch. Path. & Lab. Med.*, Chicago.)

According to recent work of Evans and Burr (1928), commercial casein, the source of the protein used in the diets which were fed to these dogs, contains the "growth-promoting" B factor but not the antineuritic vitamin. This would suggest that lack of the latter B fraction plays the etiologic rôle in the development of these sores. On the other hand, the lesions are suggestive of pellagra, which Goldberger associates with lack of the "growth-promoting" heat-stable factor in B. It is quite likely that dietary deficiency is not the only cause of these ulcers: trauma, pressure or other similar factors probably play a part. These ulcers are quite sug-

gestive of decubital lesions. In the light of these observations, these authors suggest that administration of liberal amounts of vitamin B, particularly
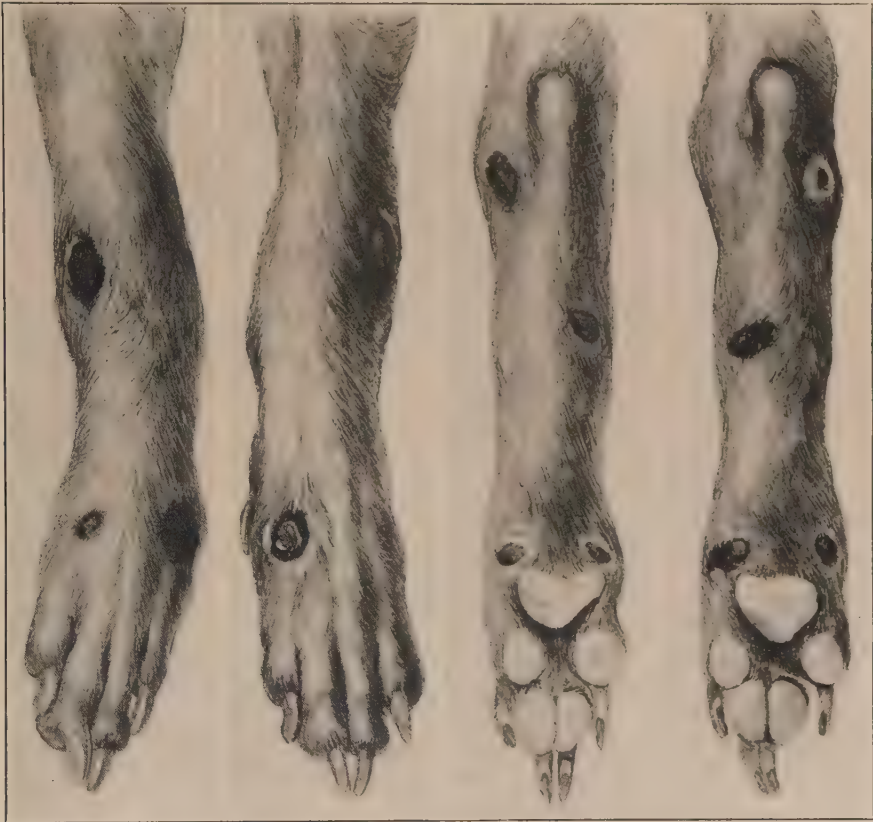
FIG. 7.—CUTANEOUS LESIONS APPEARING IN DOG ON A DIET ADEQUATE EXCEPT IN VITAMIN B. (From Cowgill, Stucky and Rose, *Arch. Path. & Lab. Med.*, Chicago.)

to cases which in the light of clinical experience are very likely to develop decubital sores, might prove helpful and worthy at least of clinical trial.

Pathology of Vitamin B Deficiency

Beriberi has been extensively studied by pathologists. In Vedder's monograph will be found an excellent review of the work done prior to 1913. The main points that have received emphasis concern what have been called degenerative changes in the nervous system, hypertrophy of the heart and anasarca. Similar nervous changes have been observed in pigeons fed polished rice, and in rat sucklings exhibiting symptoms of a lack of the antineuritic factor. More recent studies of human beriberi by Kimura (1919) show that changes occur in the brain that are held

to yield histological pictures indistinguishable from those of toxic neuritis produced by alcohol, for example.

Cramer and associates (1921) find that vitamin B deficiency in the rat brings about abnormal changes in the lymphoid tissues of the body and more particularly those tissues situated along the alimentary canal. They believe that vitamin B assumes some important rôle in the functioning of such tissues. If this vitamin is a constituent of cell nuclei, as is suggested by its distribution in nature and by what is known of its chemical behavior, then Cramer's findings are to be expected because lymphoid tissues are unusually rich in cells and nuclear material. The interpretation, however, which seeks to attribute to vitamin B a more or less *specific* rôle in relation to the functioning of lymphoid tissues in contrast to other tissues may require some modification.

The pathology of vitamin B deficiency still merits more detailed investigations.

Distribution of Vitamin B

This is the most widely distributed of any of the known vitamins. It is present to some extent in all natural foods. The foods that are noticeably lacking in this factor are the "refined" products of various kinds, such as polished rice, white wheat flour, starches, sugars, degerminated corn meal, commercial oils, lard and butter. The tissues of the body contain it, the glandular organs and organs rich in cell nuclei such as liver, pancreas, kidney and brain being richer than muscle. Fruits and vegetables may be used as sources—tomatoes, raw cabbage, fresh spinach, legumes and alfalfa containing more than such materials as orange and lemon juices, cauliflower, onions or lettuce. The nuts contain only moderate amounts. The vitamin B in egg is found in the yolk. Yeast is rich in vitamin B content but not all yeasts are of equal value. Thus, baker's yeast is inferior to brewer's yeast.

In studying tables showing the distribution of this vitamin as revealed by experiment, one should bear in mind that the test most commonly employed has been that of using the young rat, and the result, therefore, is a determination of the presence or absence of both the antineuritic factor and the "growth-promoting," substance. If an insufficient amount of either of these is present it becomes a limiting factor causing the failure of growth. As stated elsewhere, tests of different foods for their contents of each of these B fractions by suitable technic have revealed the existence of wide differences. For all practical purposes in human nutrition, the distribution of vitamin B among various foods as stated above is sufficiently accurate.

Products unusually rich in vitamin B content, in most cases representing a concentration of this factor from yeast or wheat embryo, are available to the clinician. Two points of view regarding their use have

been expressed. There are those who believe that, because vitamin B is so widely distributed among foods, and because no striking lack of this material from the average American dietary has been demonstrated hitherto, there is no justification for the clinical use of such preparations. The other view is that, although a widespread use of such materials may not be necesasary because a judicious selection of foods will suffice in most cases, it is the part of wisdom to have at hand concentrated forms of this vitamin in order that large amounts may be quickly and easily administered to selected cases. The writer subscribes to this latter view. There can be little doubt of the value, for example, of having a concentrated form of the B factor to add to the bottle milk or to be given in other ways directly to certain cases of marasmic infants. The administration of vitamin B in amounts sufficient to meet the organism's requirement may be very difficult in an individual suffering from certain types of gastro-intestinal disturbance that do not allow the ingestion of large amounts of ordinary foods. Adequate nutrition for such cases, however, just as surely requires that all of the essentials be given, a fact that clinicians as a group seem to have lost sight of. It is not at all unlikely that the decubital sores in certain patients are but expressions of the fact that a serious state of malnutrition exists due to an inability to ingest normal amounts of food, and *failure of the clinician to insure that at least the minimal amounts of all dietary essentials are taken.* The advantage of having at hand a suitable concentrated form of vitamin B for administration of this essential to such a patient is obvious. Concentrated forms of the other vitamins, as cod-liver oil, for example, have been found and are widely used. The fruit juices offer good sources of vitamin C and such sources are fluid and therefore easy to administer. Although such juices contain vitamin B, they are not rich in this substance and, unless used in large amounts, should not be relied upon alone to supply the B factor.

Clinicians desiring to use preparations that are concentrates of vitamin B should insist that they be demonstrated by biological tests to be true concentrates of this factor.

VITAMIN A

Discovery

Discovery of this accessory dietary factor was made at practically the same time (1913) by McCollum and Davis, and Osborne and Mendel, working independently. The failure of rats to grow successfully on certain artificial rations lacking fat or having some of the carbohydrate replaced by lard, led McCollum and Davis to determine the effect of adding to the diet the ether extracts of egg, butter, lard and olive oil. The prompt resumption of growth that occurred when the extract of either egg or

butter was added, was in marked contrast to the continued failure that characterized the experiments with extracts of lard and olive oil. In the experiments of Osborne and Mendel, the great superiority of diets employing milk over purely artificial food mixtures was being investigated. When butter was used in place of part of the lard in the artificial rations, the experimental animals showed prompt recovery and rapid growth.

Since the publication of these results, innumerable papers have appeared confirming these observations and supporting the thesis that normal nutrition requires, in addition to the well-known foodstuffs, minerals, vitamin B and the like, that which has been designated *fat-soluble vitamin A.*

Physiological Effects of Vitamin A Deficiency

Impairment of Growth.—Reference has already been made to the fact that the existence of vitamin A was discovered while studying the ability of certain diets to support growth in the rat. Further studies of this phenomenon have shown that the organism possesses considerable capacity for storing this dietary essential. A young animal that has subsisted on a diet rich in this vitamin, when placed on a vitamin A-free ration, may continue to grow for as long as ten weeks at a normal or nearly normal rate. When the surplus of vitamin A possessed at the beginning is presumably exhausted, growth slackens and soon ceases. The ability of the organism to store the vitamin was not readily appreciated by the early investigators. This fact, together with the fact that the ability of test rations to support growth was made the basis of the biological test of the presence of vitamin A, resulted in many tests of foods being made under unsatisfactory conditions. As a consequence, considerable confusion is found in the literature concerning the quantitative distribution of this substance in foods, its sensitivity to oxidation, etc.

Eye Disease.—An animal that has exhausted its stores of fat-soluble A apparently develops thereby a lowered resistance to disease. The first striking demonstration of this fact was seen by Osborne and Mendel (1913, 1914), who observed in their experimental animals a characteristic eye disease.

"This usually begins with a swelling of the lids of one or both eyes or with indications that the eye is becoming unduly sensitive; then there commonly develops an inflamed and catarrhal condition of the conjunctivæ with a bloody or purulent discharge, the lids becoming scabby or sticky. This, with the swelling of the lids, sometimes results in the eye being found completely closed. Often the inflammation extends to the cornea and if not treated may result in permanent blindness, though the animal often dies before the eye disease reaches this stage. The typical eye condition undoubtedly involves infection and in this sense is not purely a deficiency disease, yet it is essentially so, inasmuch as the dietary deficiency so

enormously increases the susceptibility of the animal to the infection as practically to determine the occurrence of the disease. It is also very significant that without any other treatment whatever, the eye disease if not too far advanced, usually disappears quickly when the animal is given any food containing a sufficient amount of vitamin A" (Sherman and Smith, 1922, page 189).

This eye disease has been produced experimentally not only in the rat but in the guinea-pig, rabbit, chicken, swine and dog as well. Figures 8 and 9 are photographs of a dog as it appeared before and after receiving treatment for this condition (Steenbock, Nelson and Hart, 1921).

FIG. 8.—OPHTHALMIA IN DOG AS RESULT OF A DIET DEFICIENT IN VITAMIN A. (Steenbock, Nelson and Hart, *Am. J. Physiol.*, Balt.)

The clinical literature also contains accounts of xerophthalmia in children without doubt due to lack of vitamin A. Thus, Mori (1904) observed approximately fifteen hundred cases among Japanese children between the ages of two and five years. Such cases were readily cured by administration of cod-liver oil. Of peculiar interest in this connection and a fact to which Mori called attention, was the widespread belief, among the Japanese population, in the value of chicken liver and eel fat as a remedy for this condition. This Japanese investigator was apparently the first to definitely associate

FIG. 9.—SAME DOG AS IN FIG. 8.

The ophthalmia was cured in ten days by the addition to the diet of 20 c.c. cod-liver oil per day. (Steenbock, Nelson and Hart, *Am. J. Physiol.*, Balt.)

xerophthalmia in the human subject with defective diet.

Bloch (1917, 1919, 1921) observed many cases of this disease among Danish children, and in his earlier work attributed the obvious malnutri-

tion in such cases to lack of fat in the diet. The most successful treatment consisted of administration of cod-liver oil or whole milk or cream. During the Great War, blockade of sea ports made it necessary for the Danish government to ration dairy products to the population. As a result many children, especially among the poorer classes, were being fed largely on skimmed milk and cereals prepared in various ways. An epidemic of xerophthalmia occurred. In 1918, the disease nearly disappeared following the introduction of butter into the dietary of the poorer people, this being brought about through government regulations. A photograph of one of Bloch's cases is shown in Figure 10. Similar cases of eye trouble in children responding to cod-liver oil treatment were observed by Wells, in Roumania, and Dalyell, in Vienna. These cases are reported in the paper by Blunt and Wang (1921).

Other Infections.—The lowered resistance to infections of animals deficient in vitamin A may result in the development not only of the eye disease just described but nasal sinusitis, infections of salivary glands, lungs and kidneys, and cutaneous malnutrition as well. In Figure 11 is shown a photograph of one of Osborne and Mendel's rats. In this case the effects of the vitamin deficiency are apparent in the eye, ear, nose, feet and hair. Daniels, Armstrong and Hutton (1923) report that rats given diets low in vitamin A content are prone to develop nasal sinusitis even before xerophthalmia appears. Osborne and Mendel have also called attention to the frequent presence of diarrhea and a loss of appetite as accompanying conditions.

FIG. 10.—XEROPHTHALMIA IN HUMAN INFANT.

Photograph was taken after recovery. "The child can see with the right eye which is almost normal, the left eye being for the most part leukomatous." There is total necrosis of the left cornea and less necrosis of the right. The disease arose after about two months' feeding with oatmeal. (Bloch, reproduced by the permission of the editor of the *Journal of Hygiene,* London.)

The studies of Sherman and Macleod (1925), on the relation of vitamin A to longevity in the rat, are very important in this connection, and emphasize the fact that the adult as well as the young organism has definite need for this dietary factor. The shorter life span of animals subsisting on diets poor in vitamin A and the high mortality rate associated with high incidence of pneumonia and related conditions characterizing such animals are points worthy of note. Studies of the distribution of

vitamin A among tissues of the healthy organism show that lung tissue contains a relatively large amount. It becomes possible, then, to understand why continued subsistence on a diet low or relatively free from this fat-soluble factor should result in exhaustion of tissue stores, lowered tissue resistance to bacterial invasion, and particularly a serious involvement of the nasal and pulmonary tissues.

Many clinicians have expressed the view that the ordinary mixed diet of most American and European people is on the whole satisfactory, because the deficiency diseases occur only among people whose diets are notably restricted and monotonous. McCollum (1925) has gathered together evidence from clinical literature showing that this view is falla-

FIG. 11.—PHOTOGRAPH OF A RAT EXHIBITING EFFECTS OF DEPRIVATION OF VITAMIN A.
(From Osborne and Mendel.)

cious. "As an illustration, Cramer (1924) describes epidemics of eye affections which occurred in England during the last forty years in various industrial schools. The last recorded outbreak was in 1911, and was investigated by McNeil and McGowan (1913). The condition of the children was diagnosed as 'distorted pneumonia' which varied from a fulminating, rapidly fatal type to an abortive or latent type. Special mention was made of the prevalence of a chronic granular conjunctivitis. Investigators clearly recognized the non-contagious character of the epidemic, but were unable to explain the nature of the disease or to recommend a rational treatment. From our present knowledge of quality in foods it seems highly probable that these boys were manifesting the effects of vitamin A starvation."

Recent studies of Sherman and Burtis (1928), on the quantitative aspects of vitamin A requirement, indicate very definitely that, as is the

case with vitamin B, the organism's need for this substance increases both
with increasing size of the body and with rate of growth. "With regard to
the feeding of children these facts will mean . . . that the large child
needs a liberal allowance of this vitamin because of his size and the small
child needs a liberal allowance to induce and support a rapid rate of
growth." These experiments also showed that the level of intake of vitamin
A during early life may markedly influence subsequent susceptibility
to infection.

In the light of these facts some clinicians are adopting the practice of
prescribing cod-liver oil (rich in vitamin A) not only for growing children
but for individuals who show a relatively high susceptibility to colds and
related conditions, such as bronchitis for example. Such a practice may be
regarded as justified by the scientific data at hand.

Abnormality in Estrum and Ovulation.—Evans and Bishop have been
able to show a striking relation between vitamin A and the processes
involved in estrum and ovulation. Evans has abstracted these findings
as follows:

"It has previously been shown in this laboratory that ovulation in the
rat can be detected in the living animal by a series of histological changes
in the vaginal smear, changes which are correlated with the growth, mat-
uration and rupture of the graafian follicles at periodic intervals. When
for any reason the follicles are unable to completely mature (as in animals
treated with hypophyseal substance) vaginal estrous changes are absent.
A totally different picture is produced if follicles develop but are unable
to rupture; under such circumstances, the estrous changes may be remark-
ably prolonged, and the di-estrous pause in fact obliterated. As Evans and
Long have shown, this occurs as a rare anomaly in large colonies of
animals. *But this prolongation of estrous vaginal changes and failure of
ovulation occurs in 100 per cent of animals reared on diets which are low
in vitamin A but which have nevertheless permitted preliminary normal
growth.* We have used typical diets employed by E. V. McCollum and by
T. B. Osborne and L. B. Mendel, in which the chief fat content was
furnished by lard. On the administration of small quantities of dried pow-
dered leaves of young succulent alfalfa or of small quantities of butter fat,
this characteristic abnormality in estrum and ovulation was cured." (See
Sherman and Smith, 1922, page 200.)

The attention of the reader should be called to the fact that these
phenomena occur in adult animals subsisting not on diets that are practi-
cally free from vitamin A but on rations that are low in content of this
factor, a condition that is more likely to occur in the cases observed by
the clinician.

Evans has stated his belief that the histological changes revealed by
the vaginal smear method constitute the earliest sign of vitamin A de-
ficiency, revealing such lack long before any of the other symptoms such

as xerophthalmia, nasal sinusitis and the like appear. Further discussion of this topic will be found elsewhere (see vitamin E).

Lithiasis.—In 1917, Osborne and Mendel called attention to the fact that out of 857 necropsies on their experimental animals, eighty-one cases of characteristic phosphate calculi were found. ". . . Thirty-five (43 per cent) of the rats had never received butter-fat, or any other of the fat-soluble vitamins in their rations. Of the remaining forty-six cases, none of the animals had received food known to furnish such a vitamin during the entire course of the experiment; and only thirteen had this substance during more than one-half of the period in which they were on an experimental diet. . . . In other words, *in every instance where calculi developed, the animals were without an adequate source of the fat-soluble vitamin for some time.*"

Although McCollum did not agree that such a relationship was well supported by his experimental evidence, both Fujimaki (1926), in Japan, and Van Leersum (1928), in Holland, working independently, have confirmed Osborne and Mendel. Van Leersum also found calcium deposits in the renal tubules of his animals to be of frequent occurrence; cystitis was rarely observed. This last observation is of interest because in their first communication on this subject Osborne and Mendel suggested the possibility that the development of the calculi might be related to lowered resistance to infection, as the xerophthalmia and other conditions discussed above would indicate. Recent unpublished observations from Mendel's laboratory indicate that kidney infections may occur frequently and become so pronounced as to persist for as long as three months after vitamin A administration is begun and the concurrent xerophthalmia has been cured. In one case the infection had persisted and been so extensive as to leave for detection at autopsy a kidney that was but a hollow shell filled with pus.

Frontali (1926) has endeavored to correlate such findings with the incidence of pyelocystitis in children.

Pathology of Vitamin A Deficiency

Wolbach and Howe (1925) studied the tissue changes that occur following deprivation of vitamin A and found the changes to affect primarily the epithelial structures. A keratinization of epithelial cells is the striking change observed. Readers interested in details should consult their paper.

In a similar study, Cramer and associates (1922) regard their observations as indicating the digestive tract to be the "key to the problem of the mode of action of this accessory substance." Blood studies were regarded as proving thrombopenia to be the only constant and characteristic lesion of vitamin A deficiency. Inasmuch as these findings and consequently their interpretation have not been confirmed by Bedson and Zilva

(1923), as well as other investigators, the relationship of vitamin A deficiency to blood-platelet formation can hardly be regarded as established.

The pathological changes occurring in the xerophthalmia characteristic of vitamin A lack have been studied by several pathologists. Wason (1921), Yudkin and Lambert (1922), and Mori (1922, 1923) have published detailed studies of this condition. Outstanding points of interest that merit attention are as follows: The changes begin in the lids and not in the cornea. The lacrimal glands become less active and finally fail to secrete tears. Mori attributes the subsequent changes that occur in the eyes largely to this loss of function of the lacrimal glands.

Distribution of Vitamin A

It has been estimated that cod-liver oil is approximately 250 times as rich as butter in vitamin A content. Egg yolk is a good source of this vitamin. The vitamin A content of milk, and therefore butter, has been shown to be somewhat variable and to depend upon the food ingested by the cow. Consumption of green summer pasturage increases the quantity of vitamin A in the milk secreted; the use of dried winter foods is associated with milk of lower A content. Spinach, both fresh and dried, alfalfa and tomatoes are all excellent sources of this factor. Yeast, although rich in vitamin B, is entirely deficient in fat-soluble A. Nuts and the cereal grains contain only very small amounts and the refined products such as white flour, polished rice, starch and sugars are totally lacking in this factor.

VITAMIN C

The striking rôle that scurvy has played in history as a scourge of armies, besieged populations, sea voyages and polar explorations and the pathology of this disease are ably reviewed by Hess in his monograph *Scurvy—Past and Present*. The salient facts concerning the discovery of the etiology of this disease and the properties of the vitamin involved will motivate the present discussion.

Discovery

Following suggestions from the work of Eijkman and others showing that birds develop a beriberi-like condition when fed polished rice, Holst and Frölich (1912) undertook a study of ship-beriberi, using other laboratory animals as subjects. This disease was very prevalent among the Norwegian sailors and was believed to be related in some way to the diet. The symptom-complex differed in some respects from ordinary beriberi. Instead of showing beriberi, however, guinea-pigs fed grains or bread alone finally exhibited symptoms considered to be identical with those of human scurvy. These investigators also produced scorbutic symptoms in

swine by feeding various faulty diets. In addition to the signs of scurvy, these animals developed nervous and muscular symptoms characteristic of beriberi. The complete syndrome was very similar to that of ship-beri-beri. Out of this work came the realization that ship-beriberi is probably a combination of beriberi and scurvy resulting from defective diet.

Holst and Frölich found that the addition of small amounts of fresh cabbage or carrots or other fresh vegetables cured animals suffering from scurvy. They also demonstrated that the antiscorbutic substance in the foods tested is destroyed by cooking or drying.

Since the publication of Holst and Frölich's work, a large number of investigators have been attracted to the study of experimental scurvy. It is now quite generally agreed that this disease in the guinea-pig is identical with human scurvy and results specifically from a lack of a dietary factor called vitamin C.

Scurvy has also been produced experimentally in the monkey but not in the chicken, rat or dog. Several explanations have been offered for these species differences: (1) that the immune species have a low require-ment for vitamin C and can utilize undemonstrable amounts in foods; (2) that these species have the power of synthesizing antiscorbutic sub-stance; and (3) that these species may be able to utilize a different form of the vitamin that the guinea-pig, man and monkey cannot employ. Although the immune species do not develop signs of scurvy when re-stricted to a scorbutic diet, their tissues have been shown to contain vitamin C (Parsons, 1920). Harden and Zilva (1918), and Drummond (1919) believe that "rats existing on a scorbutic diet, although capable of gaining in weight and reproducing themselves, without any apparent manifestation of pathological symptoms for months, do not thrive as well as animals which have had their diets supplemented with an antiscor-butic."

Stability and Distribution of Vitamin C

This is the most unstable of the vitamins. It is especially sensitive to oxidation. It is present in all fresh fruits and fresh vegetables. The acid fruit juices and such an acid vegetable as the tomato appear to contain the largest amounts. There is considerable evidence that the acidity of these foods exerts a protective action against oxidative changes. Vitamin C is readily destroyed by alkali. The observation that canning does not seriously diminish the vitamin C content of the tomato is of great im-portance to the housewife, dietitian and clinician because of the low cost of such material as compared with fresh fruits and vegetables, particularly during the winter season.

The prevalence of infantile scurvy and the importance of milk in the dietary of the human infant have resulted in considerable attention being devoted to the vitamin C content of this food. The ease with which the

vitamin C in milk may be destroyed is readily illustrated by the experiments of Hess, who showed that mere shaking of the milk in a half-filled container, thus mixing well with the air therein, results in almost complete loss of antiscorbutic substance. Pasteurization in the *full* bottle is therefore the correct procedure if one is to avoid loss of the vitamin C. It has been shown that the vitamin C content of milk is variable and dependent on the food eaten by the cow: Summer milk from cows receiving green food are richer in this vitamin than winter milk. In discussing these facts, McCollum makes this very important statement: "Since there is such great variation in the vitamin C content of fresh milk, it hardly seems worthwhile to emphasize to the extent that has been done the importance of preserving the antiscorbutic properties of milk. It seems best to look to other articles in the diet to supply this principle." It is an appreciation of this fact that has led many pediatricians to adopt as a standard procedure the administration of fresh orange juice or other source of vitamin C to every infant.

Vitamin C in Relation to Dentition

Studies of the pathology of experimental scurvy as produced in the guinea-pig have shown the outstanding tissue change to be one involving the intercellular matrix of connective tissue and the teeth. Zilva and Wells (1919) found the teeth to be the structure first to exhibit such changes and suggested the possibility that dietary deficiency underlies the great prevalence of caries in nonprimitive people. The recent studies of Kappes (1928) on the factors in the decay of teeth are interesting in view of this suggestion, because the only feature that seemed to have a definite etiologic significance in preventing decay in the groups of children was a diet composed largely of fruits and vegetables. Wolbach and Howe (1926) have confirmed Zilva and Wells on the main points and have observed a most remarkable and prompt change in the tooth pulp and connective-tissue matrix associated with the cure of scurvy following the administration of vitamin C.

Vitamin C in Relation to Reproduction and Lactation

Inasmuch as vitamin C cannot be synthesized in those species that are susceptible to scurvy and must therefore be furnished in the food, it might be expected that the developing young would draw upon the maternal organism for this vitamin during gestation and lactation. Ingier (1915) studied the effect of a scorbutic diet upon pregnant guinea-pigs and their unborn young. The results varied, depending upon whether the vitamin C-deficient regimen was imposed during the early or latter part of pregnancy. In the former case, the young were born dead or prematurely and gave evidence of retarded growth. In the latter case, the young

were born alive but showed signs of latent scurvy. It was also observed that pregnant females more quickly succumb to a scorbutic diet than do animals not subject to the demands of pregnancy and lactation. In Hess's opinion these phenomena have their counterpart in the human species in the miscarriages, stillbirths and congenital scurvy occurring where the mother's diet is inadequate with respect to vitamin C. The variation in vitamin C content of milk associated with the food ingested has already been pointed out, and the importance of administering to the suckling liberal amounts of some other source of this dietary factor has been emphasized.

VITAMIN D

Discovery

The existence of vitamin D was discovered in the course of studies of rickets produced experimentally in the dog and rat. The pioneer work in this field was done by Mellanby (1919), who produced rickets in numerous puppies fed various faulty diets. Figures 12 and 13 are photographs of two of Mel-

FIG. 12.—TERRIER WITH RICKETS.
(From Mellanby, Brit. M. Research Council, Spec. Rep. Series No. 61, with Permission of the Controller of His Majesty's Stationery Office, London.)

FIG. 13.—RETRIEVER WITH RICKETS.
(From Mellanby, Brit. M. Research Council, Spec. Rep. Series No. 61, with Permission of the Controller of His Majesty's Stationery Office, London.)

lanby's experimental animals exhibiting rickets. This investigator was the first to relate certain fats rich in vitamin A to the prevention of rickets. For example, he found that cod-liver oil possesses great antirachitic power; suet and butter fat are good in this respect but they are not as valuable as cod-liver oil, and lard has no antirachitic potency. Among the vegetable oils, peanut oil was found to be the most effective. Mellanby related the antirachitic power which is exhibited by these fats to a high content of vitamin A, and thus related this fat-soluble factor to rickets.

McCollum and his associates showed that cod-liver oil treated with a

stream of air bubbles at a high temperature loses nearly all of its vitamin A, being no longer able to cure xerophthalmia in rats when constituting 2 per cent of the ration. Two per cent of butter fat similarly treated brings about a cure of this eye disease within five to ten days. Two per cent of the oxidized cod-liver oil, although unable to cure xerophthalmia, proves very efficacious in healing the lesion of rickets. In view of these facts it was concluded that the antirachitic substance is distinct from vitamin A. It was called vitamin D.

Vitamin D and Its Relation to Rickets

Since the publication of the work of Mellanby in England, and that of Hess, McCollum and others in America, the study of experimental rickets has been vigorously prosecuted by a large group of investigators. The literature is very extensive. Out of all this work has come an appreciation of the fact that other important dietary factors besides vitamin D are involved in the production of rickets. It has proven possible to produce rickets by shielding the organism from sunlight or ultraviolet rays and feeding diets (1) deficient in vitamin D, normal or high in phosphorus but low in calcium; and (2) deficient in the D factor, normal or high with respect to calcium but low in phosphorus. In other words, the amounts of calcium and phosphorus available in the diet and the relative amounts, or calcium-phosphorus ratio, are very important. Vitamin D apparently enables the organism to utilize amounts of calcium in the diet that would otherwise be too small.

Radiant energy, represented by sunlight and more particularly by the short wave lengths in the ultraviolet range, exerts a curative action on rickets. Thus, Hess observed healing to occur in a group of children receiving some exposure to sunlight; another group in the same institution was confined indoors and received light that had passed through glass windows, and in this group recovery from rickets was not as satisfactory. Subsequent to this observation rats were placed on a rickets-producing diet and the ability of sunlight to prevent the development of the disease was demonstrated. Further experiments of this sort showed that *exposure of the organism to radiant energy of the proper wave length (ultraviolet range) is the physiological equivalent of the administration of vitamin D.*

Studies endeavoring to elucidate this relationship have yielded many remarkable facts. Steenbock and Black (1924), and Hess (1924), working independently, found that rat rations, shown by repeated tests to be productive of rickets, could be endowed with antirachitic power by irradiation with the mercury vapor quartz lamp. In other words, some substance —or substances (?)—in the rations was activated by the radiant energy and presumably changed to vitamin D. Irradiation tests with pure proteins and pure carbohydrates yielded negative results. Nearly all fats so treated

acquired antirachitic power. Attempts to isolate vitamin D showed that this substance resists saponification with alcoholic potash solution. This fact suggested that vitamin D belongs to the group of compounds known as *sterols*. The most common sterol found in animal tissue is cholesterol. Irradiation of this substance by ultraviolet light causes it to acquire antirachitic power, suggesting that this substance is the precursor of vitamin D. Certain data, however, suggested that some impurity in cholesterol might be the provitamin. By means of chemical and spectroscopic analyses it has been possible to show that another sterol, *ergosterol,* closely allied to cholesterol and present as an impurity in the cholesterol preparations used, is the substance activated by ultraviolet light and, in all probability, the substance sought after.

Hess and Lewis (1928) have published figures that are interesting in this connection. "Activated ergosterol is perhaps two thousand times as potent as activated cholesterol, and a hundred thousand times as potent as cod-liver oil, and is able to prevent or cure rickets in rats in a daily dose of 1/20,000 Mg., or less, according to the purity of the preparation. Notwithstanding the attainment of this high degree of potency, it is probable that only a small amount of the ergosterol is rendered active by irradiation, probably not more than from one to two per cent."

In applying these facts to the clinic certain additional considerations should be borne in mind. It has been shown that the amount of the curative ultraviolet wave lengths present in sunlight varies with season, geographical location, and time of day. Proper use of this therapeutic agent requires that this fact be taken into account. The mercury vapor quartz lamp may be used and thus the extent of irradiation of the subject much more adequately controlled. The recommendation of students of nutrition that liberal use be made of milk, because it represents probably the cheapest rich source of calcium and phosphorus required for bone development, should be followed. Discovery of the remarkable efficacy of irradiated ergosterol in preventing and curing rickets places in the hands of the clinician a therapeutic agent of great value. Whether this should be used instead of a tested cod-liver oil or liberal quantities of D-rich foods, as egg yolk, for example, will depend upon the judgment of the clinician with respect to the case in question and relative costs.

VITAMIN E

The relations between fertility and nutrition with particular reference to vitamin E are discussed in detail by Evans in his Mayo Foundation Lecture (1925). In the following paragraphs are presented the outstanding facts of interest. The reader is referred to the papers by Evans and his associates for detailed amplification of these points.

Discovery

This substance was discovered by Evans and Bishop in the course of investigations designed to determine why reproduction failed in rats subsisting on certain experimental diets. Reference has already been made to the development of a so-called vaginal smear method whereby histological changes correlated with growth, maturation and rupture of the graafian follicles may be followed. The essential facts concerning these changes in the rat as revealed by this method may be summarized as follows (Evans, 1925):

"Irregularly shaped, small, nucleated epithelial cells mixed with leukocytes constitute the picture found in the resting stage. Preparatory to estrum and ovulation, there is a sharp pause or halt in the immigration of leukocytes which usually creep in considerable numbers from the subjacent capillaries through the epithelial cells of the vaginal mucosa into the lumen. Leukocytes are suddenly no longer encountered in the smear. Epithelial cells alone, a peculiar type of them, sometimes in sheets, are now found. Quickly succeeding this change come non-nucleated, transparent cornified cells, sooner or later in similar sheets. A massive production of these cells takes place, so that macroscopically a cheesy detritus is found. Eventually leukocytes again recur and quickly thereafter are found in enormous numbers. The cornified epithelial cells give way to scanty small nucleated ones. This is the cycle of changes. The presence of true cornified cells, singly or in sheets, is a reliable criterion for impending maturation of ova and consequent rupture of graafian follicles in the ovary."

In vitamin A deficiency, use of this method reveals that the tendency of the vaginal mucosa to form cornified epithelial cells is no longer limited, as is normally the case, to the time of growth, maturation and rupture of the graafian follicles, but is continuous, thus obscuring all ovarian cycles that may also be present. This variation, constituting a prolongation of the estrous changes, is given by no other food deficiency so far studied. What is equally striking is the fact that amounts of vitamin A just sufficient to prevent the development of xerophthalmia and to allow growth may be fed and the amount still be too small to abolish this sign of prolongation of estrum. Increasing the amount of vitamin A administered immediately abolishes this sign.

The striking phenomenon characteristic of deficiency of vitamin E is the fetal death and absorption that occurs at some time between the twelfth and twentieth days of gestation, usually on the twelfth or thirteenth day. For some days thereafter, however, the maternal part of the placenta continues to live, and this would appear, according to Evans, "to speak decisively for peculiar need on the part of the developing young for the new vitamin as against placental injury as the cause of death." Females

that have exhibited a typical resorption are used in determining whether
a given food contains vitamin E. Shortly after the incomplete or resorp-
tion gestation, a small amount of a single natural food is now added to
the ration or fed separately from it, and the fate of the new gestation
followed with similar care. If vitamin E has been given, a normal sized
litter of vigorous young results; if not, another resorption gestation
occurs. In this way the distribution of vitamin E among various foods
is determined.

Facts Concerning Vitamin E

This substance is present but never highly concentrated in a great
variety of animal tissues. Muscles are richer than viscera. Milk fat con-
tains only a small amount. Cod-liver oil, although rich in vitamins A and
D, is lacking in the E factor. In contrast to these foods of animal origin,
vitamin E is much more abundant in certain plants, especially in seeds
and green leaves. Cereals contain large amounts of vitamin E. In the
wheat cereals it is low in the endosperm but concentrated in the embryo.
Of all the natural substances tested, none was found to equal wheat
embryo in curing resorption gestation. Evans and his associates have
been able to secure by ether extraction of wheat germ and carefully dried
lettuce leaf oils so rich in vitamin E that one drop per day (25 Mg.)
proves efficacious in curing this type of dietary sterility. Curative foods,
or extracts of those foods, can be fed as late as the fifth or sixth day of
pregnancy and the developing young can be saved. The vitamin in the
form of oil can be just as effectively administered parenterally (subcu-
taneously or intraperitoneally) as by mouth.

"Vitamin E is transferred from mother to offspring during intra-
uterine life, for the tissue of newborn rats cures female dietary sterility."

There is some storage of vitamin E. This is evidenced by the fact that
if animals reared on a diet of natural foodstuffs and demonstrated to be
fertile are shifted to a ration deficient in vitamin E, they preserve their
fertility for three or four months and then lose it. "Similarly, when sterile
animals are cured with foods containing the vitamin, the length of time
over which fertility is normal is found to be roughly dependent on the
amount of vitamin E administered."

Lack of vitamin E affects not only the female but the male as well
(Mason, 1925). In the male it eventually leads to destruction of the germ-
cells and finally, the entire seminiferous epithelium. Such is not the
case with the female; the ovary and ovulation are unimpaired throughout
life. The characteristic disturbance in the case of the female occurs during
gestation and consists in the death and resorption of the developing young.

There is evidence that vitamin E is employed in other metabolic
processes in the body besides those associated with gestation. Females
demonstrated to be fertile and then shifted to a vitamin E-deficient diet

become sterile in time, whether protected from the drain of reproduction, and especially placental function, or not.

Vitamin E is remarkably resistant to heat, light, air and many of the ordinary chemical reactions. It may be called fat-soluble, though, as Evans remarks, "its range of solubility is far greater than that of ordinary fats."

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CHAPTER VI

LOCAL IMMUNITY

Harry Plotz

GENERAL CONSIDERATIONS

Local immunity, as described by Besredka, may be defined as an immunization of the receptive cells, which is brought about by the direct action of the immunizing agent with these cells. The receptive cells are those cells for which the immunizing agent has the greatest affinity. The immunity following local immunization is brought about without the presence of demonstrable antibodies.

The accepted theory of the mechanism of immunity is unsatisfactory in explaining many of the phenomena which occur. The immunity which follows an attack of typhoid fever cannot be explained on the theory of antibody production alone, for these antibodies soon disappear after an attack of the disease while the individual remains immune. Likewise, individuals immunized with dead typhoid bacilli often show the presence of antibodies, but may go on to develop a fatal attack of the disease in spite of them. The immunity following vaccinia is durable, still the presence of antibodies cannot explain it. Patients infected with tuberculosis may show a high titer of antibodies, and still go on to a fatal issue. Neither the streptococcus or staphylococcus antiserum is of great value in the treatment of these infections, and still these sera contain specific antibodies. These are only a few of the questions which make one think that there are factors, other than the presence of antibodies, that are responsible for the immunity produced.

Since the purpose of this article is to present the therapeutic applications, based on the principle of local immunity, this is not the place to cite all the laboratory findings which led up to the present concept of local immunity. It is, however, necessary to state the basic facts, in order that the principle may be understood.

While Pasteur had succeeded in immunizing sheep against anthrax infection, no one had succeeded in immunizing the guinea-pig or rabbit against this disease. The inoculation of dead bacilli in these animals, even in large quantities, produced antibodies, but these animals could not resist the inoculation of a fatal dose of virus. Likewise, the subcutaneous inoculation of either the first or second Pasteur vaccine could not be employed

in vaccinating laboratory animals, because they always died of the infection. This susceptibility of the guinea-pig and rabbit for the anthrax bacillus was explained on the basis that these animals were unable to build up any resistance to this bacterium.

Besredka [1,2] showed that it was possible to vaccinate these laboratory animals. His experiments demonstrated that the skin cells were the receptive cells for the anthrax bacillus. If due precaution is taken, and it should be noted that this is often technically difficult, large doses of virulent anthrax bacilli, or virulent blood obtained from an animal dead of the disease, may be inoculated subcutaneously, intravenously, or intraperitoneally, and the animal does not become infected. In this instance, these virulent bacilli act as if they were non-pathogenic. No infection and no immunity follows. An anthrax infection in guinea-pigs and rabbits, may only be produced by skin infection. When the skin is infected, the animal always dies of a typical anthrax infection. Since it is only possible to produce typical anthrax by skin infection, Besredka thought that the immunization should be by way of the skin also. It has been shown that when the first anthrax vaccine is rubbed into a shaved area of skin or inoculated directly into the skin, the animal will subsequently develop a resistance to an intradermal inoculation of the second anthrax vaccine, which, when inoculated in normal animals, kills them. Following the inoculation of the second vaccine, large doses of virulent anthrax bacilli may be inoculated into the skin and the animal will survive. It is shown, then, that the skin cells are the receptive cells. These are the only cells that may be infected and the only ones that may be immunized. Following skin immunization, large doses of virulent bacilli may be inoculated in any part of the animal body and the animal will resist the infection. It should be noted that no antibodies are produced following skin immunization. [3]

Balteano (*Compt. rend. Soc. de biol.,* Par., 1922, 87 : 653, 655) confirmed these findings in the guinea-pig and rabbit; Vallée (*Bull. Soc. centr. de méd. vét.,* Paris, 1923, p. 285) showed skin sensitivity in the ox, while Mazucchi (*Clin. vet.,* Milano, 1923) observed the same in sheep. Boquet (*Compt. rend. Acad. d. sc.,* 1924, 178 : 260) showed that anthrax bacilli may appear in the blood stream following their feeding. Guinea-pigs that have been fed anthrax bacilli do not die, but when a cardiac puncture is made, in order to obtain a blood culture, the animal dies with a typical

[1] *Local Immunization,* Williams and Wilkins.

[2] *Études sur l'Immunité dans les Maladies Infectieuses,* Masson et Cie.

[3] Gratia (*Compt. rend Soc. de biol.,* 1924, 91:795,) reports having found agglutinins and protective properties in the serum of guinea-pigs cutaneously vaccinated. In examining these results we find that this worker inoculated the serum to be tested and the virus in mixture. It is known that serum has a deleterious effect upon the anthrax bacillus, and the results obtained by Gratia may be explained on this basis. For when the serum to be tested is inoculated in one part of the animal body and the culture in another, no protection follows.

anthrax edema at the site where the needle punctured the skin. This minute skin lesion was sufficient to localize the infection. Plotz (*Compt. rend. Soc. de. biol.,* 1924, 90 : 849; *Ann. de l'Inst. Pasteur,* Par., 1926, 40 : 923) showed that large quantities of virulent anthrax bacilli, contained in glass capsules, and implanted under the skin, may be liberated without causing infection in the rabbit, provided the skin is healed before the bacteria are set free. Likewise animals who have survived this inoculation showed no immunity to a subsequent inoculation of virus into the skin. Brocq-Rousseu and Urbain (*Bull. Soc. centr. méd. vét.,* Par., 1924, 99 : 482) demonstrated skin sensitivity and the possibility of immunizing horses by intradermal inoculation.

Sani (*Clin. vet.,* Milano, 1925, p. 485) claims to have induced anthrax infection in dogs by testicular inoculation. This worker also claims to have obtained an immunity in dogs who have survived a subcutaneous inoculation of virus. These results are not in accord with those obtained by others.

Adelheim and Kaktin (*Klin. Wchnschr.,* Berl., 1924, 3 : 1921) claim to have induced anthrax infection in rabbits following brain inoculation of virus. The animals died in twenty-four to thirty hours after the inoculation. At autopsy, anthrax bacilli were found in the brain, but none were isolated from any of the other organs. This can hardly be considered an anthrax infection. An animal dead of anthrax usually shows an edema at the point of inoculation and bacteria throughout the animal organism. Cernainu and Suhatzanu (*Compt. rend. Soc. de biol.,* 1924, 90 : 869) also report inducing infection following brain inoculation. In these experiments such large skin lesions were made that it appears quite evident that the skin was infected. We should recall the experiments of Boquet, cited above, where even a needle puncture in the skin was sufficient to localize an infection. If the testicle and the brain are also susceptible to anthrax infection, why is it, that after skin immunization, any quantity of anthrax bacilli may be inoculated into these organs without producing the disease? [4]

Anthrax then may be regarded as a typical example of local immunization. In this instance, the skin cells are the receptive cells. It is there that the infection and the immunization takes place. This immunity is brought about without the presence of demonstrable antibodies.

Intracutaneous immunization has been employed, with success, in vaccinating large animals against anthrax. Nicolas (*Rev. Veter. Milit.,* 1925,

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[4] Gay (*The Newer Knowledge of Bacteriology and Immunology,* Jordan and Falk) claims that, "the reason these areas [skin] are particularly susceptible, is simply because they are relatively free from phagocytes. This allows vegetative anthrax bacilli sufficient time to become animalized or encapsulated and thereby virulent." If this explanation were true it would not explain the specific skin affinity for filtered anthrax edematous fluid, which contains no bacteria. With this fluid, guinea-pigs are immunized after intracutaneous, but not after subcutaneous inoculation.

9 : 54) had excellent results in horses and mules. Of 8912 horses and mules vaccinated in Syria, there were four deaths. Two occurred during the course of the immunization and two later. This is an incidence of 0.45 per 1000. The incidence of anthrax in horses in this region was 8.1 per 1000 over a period of five years. The following year, Nicolas immunized 6994 horses and mules. There were five deaths amongst these vaccinated animals, which this worker regards as remarkable because of the large amount of anthrax in the region. In comparing these results, it should be recalled that immunization of horses by the subcutaneous route was often dangerous, for horses often died of the inoculations.

Velu and Monod (*Compt. rend. Soc. de biol.,* 1924, 90 : 746; 1925, 92) have vaccinated sheep, oxen, pigs and horses by the intracutaneous method. These workers inoculated 14,405 oxen, 12,520 sheep, 4640 pigs and 75 horses in 1924, and since then have made more than 500,000 vaccinations in Morocco. These are briefly the results obtained. A single intradermal inoculation of vaccine produces no temperature, or a local or general reaction. A solid immunity follows, which is acquired almost immediately following the vaccination. This is demonstrated by the rapidity with which animals are protected in the presence of an epidemic. One-fifth of the vaccinating dose employed by subcutaneous vaccination is sufficient to induce a solid immunity, when the inoculation is made intradermally. These vaccinated animals will resist 1000 fatal doses of virulent anthrax bacilli when inoculated intradermally. The immunity is durable, for in the vaccinated animals practically no infection has occurred, even though these animals were in an infected area, or in a region where anthrax was epidemic.

The streptococcus and the staphylococcus also have an affinity for skin cells and mucous membranes.

Besredka's experiments on laboratory animals have shown that, while killed staphylococcus cultures, injected subcutaneously, may confer a certain degree of immunity, inoculations made into the skin confer a much higher grade of protection. Killed streptococcus cultures injected subcutaneously confer no immunity, while these cultures injected into the skin confer a certain degree of immunity. In both instances, when large areas of skin are immunized, a higher degree of protection is obtained. The intensity of the immunity in this instance may be comparable to the findings of Plotz (*Compt. rend. Soc. de biol.,* 1927, 97 : 55), who showed that the degree of immunity in vaccinia depends upon the area of skin vaccinated. With both the staphylococcus and the streptococcus, a bacterial filtrate protects in the same manner as the killed organisms. In this instance, as well as with killed cultures inoculated into the skin, the immunity is induced after twenty-four hours, and hence precludes the participation of antibodies.

These experimental facts were confirmed by Urbain (*Compt. rend. Soc. de biol.*, 1924, 91), Brocq-Rousseu, Forgeot and Urbain (*Compt. rend. Soc. de biol.*, 1923, 89 : 219), and Frans de Potter (*Compt. rend. Soc. de biol.*, 1923, 89 : 828) and others. Carrère (*Ann. de l'Inst. Pasteur, Par.*, 1925, 39 : 67) showed the specific immunizing effect of bacterial filtrates in experimental infections of the eye.

The ability of the streptococcus, isolated from cases of erysipelas, to induce a local skin immunity has long been known (Meierowitsch, *Centralbl. f. Bakteriol., ref.*, Jena, 1883, 3 : 406). Gay and Rhodes (*J. Infect. Dis.*, Chicago, 1922, 31 : 101) corroborated these findings and made the interesting observation that animals protected by intracutaneous inoculation were not immune to an intravenous inoculation of virus, and that the reverse also held true. Gay (*J. Immunol.*, Balt., 1923, 8 : 1) in another series of experiments, found that, besides the observations quoted above, an injection of virus into the pleural cavity protected against an inoculation in the same region, but not by intravenous inoculation, and that the reverse was also true. Gay concludes that there is a local immunity in association with a general immunity. It should be noted that Gay's (*The Newer Knowledge of Bacteriology and Immunology*, Jordan and Falk) conception of local immunity is that it "rests on the demonstration that a given area of the body may be protected by the topical application of a given antigen without involving a more generalized immunity." This differs from Besredka's conception, in that the latter believes that once all the receptive cells are immunized the entire animal becomes immunized also. The immunity in this instance is brought about without the participation of antibodies.

Besredka has called these bacterial filtrates "antivirus." These filtrates are prepared by growing the bacterium in a broth medium for ten days and then filtering this through a Chamberland filter. This is repeated twice. The filtrate inhibits the growth of the homologous strain of bacteria, and is capable of inducing a specific immunity in animals.

Besredka's experimental results with filtrates have not been confirmed by Gay and Morrison (*J. Infect. Dis.*, Chicago, 1923, 33 : 338), Rivers and Tillett (*J. Exper. M.*, N. Y., 1925, 41 : 185) or Mallory and Marble (*J. Exper. M.*, N. Y., 1925, 42 : 465).

THERAPEUTIC APPLICATION

Bacterial filtrates, or antivirus, have been employed in therapeutics. The efficacy of these filtrates in medical and surgical practice is indicated by their extensive use. A review of the extensive literature would be out of place here. All that we can do is to indicate the conditions in which favorable results have been obtained. In examining the case reports one is struck by the rapidity and efficiency with which the antivirus works.

It should be noted that all of these observations were made by clinicians and surgeons working in various clinics.

Superficial Infections.—The application of a staphylococcus filtrate in cases of furunculosis is marked by a rapid disappearance of the pain, and a rapid development and cicatrization of the wound. Furuncles in diabetics respond favorably. In multiple furunculosis the infection does not spread to the surrounding tissue. Favorable results are obtained in furuncles of the face or external auditory canal. Boils, paronychia, breast abscess, infection of the middle ear, and acute and chronic osteomyelitis—infections usually caused by the staphylococcus, respond in an excellent manner to the local application of dressings wet with a staphylococcus filtrate. Moritsch and Oppolzer, in Eiselberg's clinic, treated a number of cases of surgical infection with success, as did Bass, Saupault and Brouet, in Hartmann's clinic. Cacan and Epstein and Lotheissen, in Vienna, as well as Feurabend, in Prague; Bourdenko and Giwago and Nikolaew, in Russia, and Helsmoortel, in Brussels, report on a series of staphylococcus and streptococcus infections treated successfully. Feldstein reports twenty-five cases of furunculosis of the external auditory canal with excellent results.

Latil, in Marfan's clinic, employed the antivirus in treating various skin infections in children, caused by the streptococcus and staphylococcus. Cases that resisted various forms of treatment responded favorably, and were cured by the use of the bacterial filtrates. Canelli, in Torino, met with the same results.

In dermatology, Löwenfeld reports on the successful treatment of twenty dermatological cases, while Meyer cured two cases of sycosis which had resisted all other treatment.

Bacterial filtrates have been successfully employed in various forms of oral infections, such as stomatitis, gingivitis, pulpitis, periostitis and maxillary infections.

Cases of ozena have yielded to a specific bacterial filtrate. These infections are particularly resistant to all forms of treatment.

Rieux and Clavelin and Marmasse report excellent results in cases of streptococcus pleurisy.

Specific bacterial filtrates are now being employed in various forms of eye infections. Many of these chronic infections that resisted all other forms of therapy reacted to the filtrates. Cases of infected wounds of the cornea, chronic abscess of the lacrimal sac, dacryocystitis and ulcerous blepharitis were successfully treated. Kissine had 92 per cent of cures in 150 cases of ulcerous blepharitis.

Bacterial filtrates, made with the colon bacillus, staphylococcus and streptococcus have been employed in various genito-urinary infections—cystitis, pyelonephritis. Legueu treated forty-two cases of pyelonephritis with the following results:

	Cures
26 cases Colon Bacillus	22
10 cases Staphylococcus	6
1 case Streptococcus	0
1 case Colon, Streptococcus, Pyocyancus	0
4 cases Colon, Staphylococcus	3

Levy-Solal reports a series of cases of puerperal infection treated by specific streptococcus filtrates. In most of the cases, the streptococcus was isolated from the lochial discharge, while in two cases the hemolytic streptococcus was isolated in blood culture. Intra-uterine dressings were applied in all the cases. All recovered. Following the application of the dressing, there usually was an improvement in the condition; most often after the third dressing there was a sharp drop in temperature and a rapid improvement. Even though three of these cases began treatment after the sixth to the eighth day, recovery was reported.

Ravina reports on a series of 4200 deliveries, where the antivirus was employed. In this series, there were seventeen cases of difficult delivery and subsequent infection with streptococci in the lochial discharge. A bacterial filtrate, made with strains of hemolytic streptococci isolated from cases of puerperal infection, was employed by intra-uterine dressings. Of this series, there were three cases where the temperature dropped after the third intra-uterine dressing. All the cases recovered. There were thirty-one cases of puerperal infection—four of whom had positive blood cultures; all recovered. There were twenty-seven postpartum streptococcus infections—the filtrate being employed by intra-uterine dressings. The temperature dropped after the second or third dressing, and all the cases recovered. There were five cases where the treatment was employed late, or one week after delivery. In these serious cases, usually with a fatal outcome, there were three recoveries and two deaths.

We have reviewed, very rapidly, a series of various types of infections, where specific bacterial filtrates were successfully employed. It should be noted that in many of these cases of chronic infection all forms of treatment had previously been employed without success. The striking results in puerperal infection, in particular, demonstrate the definite action of the filtrate.

We must now consider a group of bacteria which have an affinity for intestinal cells—*Bacterium dysenteriæ* (Shiga's bacillus), *Bacillus typhosus* and *Vibrio choleræ*.

Bacterial Dysentery.—The Shiga bacillus, either living or dead, produces typical intestinal lesions, irrespective of the method by which the rabbit is injected. Bacilli may be found in the intestine even after subcutaneous injection. Considering the intestinal cells as the receptive cells, Besredka attempted immunization by the ingestion of the virus. It was

found that rabbits could be immunized by the oral route. This immunity was solid, for these animals resisted an intravenous inoculation of virus. Confirmation of these experimental facts has since been made by Violle (*Bull. Acad. de méd.,* Par., 1921), Combiesco (*Compt. rend. Soc. de biol.,* Par., 1922, 87), and Dumas and Combiesco (*Compt. rend. Acad. d. Sc.,* Par., 1922, 175 : 652).[5]

Shiga (*Sackingaku Zasshi,* Tokio, 1908, p. 138) had already shown that it was possible to immunize rabbits by the ingestion of dead bacilli. Animals immunized *per os* showed an intestinal immunity, but developed nervous symptoms following inoculation of virus intravenously. Chvostek (*Wien. klin. Wchnschr.,* 1908, No. 14) showed that the feeding of living or dead bacilli induced an immunity to an intravenous inoculation of virus. Dopter (*Compt. rend. Soc. de biol.,* 1908-1910) showed that mice and rabbits could be immunized by the oral route.

Following Besredka's experiments on rabbits Ch. Nicolle and E. Conseil (*Compt. rend. Acad. d. Sc.,* Par., 1922, No. 11) attempted oral immunization in man by feeding two volunteers with dead Shiga bacilli. These vaccinated individuals and two volunteer controls were then given living Shiga bacilli by mouth. The vaccinated resisted, while the controls contracted typical Shiga dysentery, with bacilli in the stools.

Oral immunization against dysentery has now been employed on a large scale. Anglade (*Compt. rend. Soc. de biol.,* 1924, 89 : 395) employed oral vaccination in a garrison during an outbreak of dysentery. There were 546 soldiers vaccinated orally and 586 acted as controls. Of the vaccinated, forty-two contracted the disease, while amongst the unvaccinated, 235 contracted Shiga dysentery. Antonovsky (*Compt. rend. Soc. de biol.,* 1924, 110 : 564) vaccinated 1000 individuals in a refugee camp where dysentery was prevalent. Of the vaccinated, twelve contracted the disease, while amongst the unvaccinated (1768 individuals), fifty-six contracted Shiga dysentery. Troude (*Rev. d'hyg.,* Par., 1925, 17) vaccinated 3000 soldiers in the Rhine Army of Occupation. He reports no cases of dysentery amongst the vaccinated, while there were 471 cases of dysentery reported in this area. Maitra (*Indian M. Gaz.,* Calcutta, 1926, 6 : 334) vaccinated part of the population by the oral method and left the other part to serve as controls. All the inhabitants lived under identical conditions. There were 1136 vaccinated and 5569 unvaccinated. Twenty-nine amongst the vaccinated contracted the disease, while 284 of the unvaccinated contracted Shiga dysentery. Gauthier (*Bull. Acad. de méd.,* 1924, 91 : 72) representing the medical section of the League of Nations, carried

[5] Gay (Jordan and Falk) calls attention to the susceptibility of the central nervous system to the Shiga bacillus, and says that it might equally well designate this locality as the most vulnerable point. When a fatal dose of Shiga bacilli is inoculated intravenously, cultures made at autopsy show the presence of bacilli in the intestine, but none are found in the brain. The nervous symptoms are due to a localization of toxin and not bacteria.

on a valuable experiment in Greece amongst 30,000 refugees. These refugees were divided in many camps. All the refugees at Phalere were vaccinated orally. Following vaccination, these refugees were moved to another camp where dysentery was epidemic. There were 340 cases of Shiga dysentery reported. The vaccinated and unvaccinated lived under identical conditions. Although there was dysentery about them, not one of the vaccinated individuals contracted the disease. At Kokinia there were 400 cases of dysentery amongst a group of 4800 refugees. Two-thirds of this group were vaccinated and one-third remained as controls. There were no cases amongst the vaccinated, while amongst the unvaccinated there were 194. It should be noted that the epidemic continued for some time after the vaccination and that all the refugees lived under identical conditions.

Considering that immunization by the subcutaneous inoculation of a Shiga vaccine is impossible, because of the severe local and general reaction, the results given above indicate the importance of oral immunization in dysentery. The results in various epidemics show that oral immunization against Shiga dysentery is simple, devoid of all reactions, and efficacious.

Typhoid Fever.—Man contracts typhoid fever by oral infection. The only experimental animals that may be given typhoid fever *per os* are the higher monkeys. This was shown by Metchnikoff and Besredka (*Ann. de l'Inst. Pasteur,* Par., 1911, p. 193). During the course of these experiments, it was shown that monkeys that had contracted the disease by oral infection were immune. It had previously been shown by Loeffler (Lenthold-Festschrift 1) and Wolf (*München. med. Wchnschr.,* 1908, No. 6) and more recently by Webster (*J. Exper. M.,* N. Y., 1924, 39 : 129) that white mice could be immunized following the oral administration of dead bacilli. Kutscher and Meinicke (*Ztschr. f. Hyg. u. Infections. Krankh.,* Leipz., 1906, 62 :301) succeeded in conferring an immunity in guinea-pigs following the ingestion of paratyphoid B bacilli. Following the demonstration of the production of typhoid fever in monkeys, Courmont and Rochaix (*Acad. d. Sci.,* Par., 1911) succeeded in conferring an immunity in rabbits by oral and rectal administration of dead bacteria. Lumière and Chevrotier (*Acad. d. Sci.,* Par., 1914, 158 : 197) showed that it was possible to immunize man by oral vaccination.

While studying the mechanism of typhoid infection in animals, Besredka noted that rabbits were resistant to the oral administration of living and virulent paratyphoid bacilli. These animals did not develop typhoid fever, as he had noted in monkeys, or as was his experience in inducing dysentery in rabbits. If, however, a dose of bile is given the rabbit and this is then followed by the ingestion of living bacilli, definite intestinal lesions may be produced. No immunity is produced in rabbits who

have ingested living bacilli alone, but a definite immunity follows if living or dead bacilli are given after the previous ingestion of bile. In these instances, where an immunity is produced, it is to be noted that it occurs without the participation of antibodies.

While Zingher and Soletsky (*Proc. N. York Path. Soc.*, 1920, 20:133), Neri (*Bull. Inst. Sieroterap. Milanese,* 1922, 2:275), Glotoff (*Compt. rend. Soc. de biol.,* 1923, 89:368) and Sedan and Hermann (*Compt. rend. Soc. de biol.,* 1924, 90:567) have succeeded in producing intestinal lesions, Zingher and Soletsky, and Neri have failed to induce an immunity in the rabbit.

Following the experiments reported above, a number of workers attempted immunization in man by the oral method. The large experience now acquired with the subcutaneous method has shown that this method is efficacious. But is it as efficacious as is usually believed? The following figures are taken from the results obtained in one laboratory at Verdun during the World War. Four hundred and sixty-nine French soldiers who were completely inoculated by the subcutaneous method contracted typhoid fever. One hundred and ninety-seven developed the disease during the first six months after the inoculations. In every instance, in this series, the cases were diagnosed by the presence of a positive blood culture.

The results of oral immunization in the following epidemics are not given to prove that oral immunization is better than the subcutaneous method. They simply indicate that oral immunization in man is possible, and that the results obtained are at least as good as the subcutaneous method. The results in the future may be better when larger doses of dead bacteria are ingested. It may be said, however, that oral immunization is devoid of all disagreeable symptoms, local or general. This fact is of importance in administering vaccine to patients suffering from tuberculosis, kidney disease, heart disease, or in pregnant women—conditions where the subcutaneous method is regarded as harmful.

An epidemic of typhoid fever broke out in a military school. Two hundred and sixty-eight were immunized by the oral method and two hundred and fifty-three by the subcutaneous. The epidemic continued throughout the period of immunization. Five cases developed in those orally vaccinated, and ten amongst those who received the subcutaneous injections.

In an epidemic occurring at Moreni, Roumania, 8673 individuals were vaccinated by the subcutaneous method, 2286 were vaccinated orally and 5575 acted as controls. Of the first group of 8673 individuals, 1434 received only one injection, 2693 received two and 4546 received three injections. Of 2286 individuals who received the oral vaccine, 314 ingested the vaccine once, 372 twice and 1600 three times. The results after six months were:

	Cases of Typhoid	Deaths
5575 non-vaccinated	90	6
2286 vaccinated *per os*	6	0
8673 vaccinated subcutaneously	3	3

Tron, in Milan, vaccinated 71,131 individuals by the oral method and 38,655 acted as controls. There were 0.025 per cent amongst the vaccinated and 0.088 per cent amongst the unvaccinated who contracted the disease.

In Lodz, Poland, 28,166 individuals received oral immunization. Amongst these, fifty-two cases of typhoid fever were reported. Of these, three cases were found infected during the first week, or in individuals who had received the vaccine during the incubation period; six other cases occurred in subjects vaccinated more than a year previously. There were, then, forty-three cases of typhoid fever or a morbidity of 0.15 per cent. The controls were chosen from those individuals that inhabited houses where at least one case of typhoid fever occurred. There were 73,494 such individuals, amongst whom there were 993 cases of tyhpoid fever, or a morbidity percentage of 1.35. The morbidity amongst the unvaccinated then was about nine times more than amongst the vaccinated. In examining the results of this epidemic, it is interesting to note that there were 27 houses where all the occupants were immunized orally, or 4165 individuals. Of this number, only one person contracted typhoid fever—and in this case the disease was diagnosed one week after vaccination.

An epidemic of typhoid fever occurred at San Paolo, in Brazil. Ten thousand persons were vaccinated by the subcutaneous method and twenty-eight thousand orally. Eighty-four cases of typhoid fever occurred amongst this number. Of this group, fourteen cases occurred one year after the vaccination, twenty-five were incompletely vaccinated, while in fourteen no definite information could be obtained as to the method which was employed. There remain then thirty-one cases of typhoid fever that could be analyzed. Of these, twenty were vaccinated by the subcutaneous method, ten by the oral method, and one by both methods.

The possibility of oral vaccination against typhoid fever is indicated by these results.

Cholera.—The *Vibrio choleræ* also shows an affinity for intestinal cells. Buchner (*Arch. f. Hyg.*, München & Berl., 1885, 3 : 361, 400) calls attention to the presence of *Vibriones choleræ* in the intestine following an intraperitoneal inoculation. This fact was denied by Wyssokowitsch (*Arch. f. Hyg.*, 1885, p. 26). Cunningham (*Scient. Mem. Med. Off. India*, Calcutta, 1886) found vibriones in the intestine of guinea-pigs following intraperitoneal inoculation, but this observation was denied by Baumgarten (*Jahresb. d. path. Mikroörg.*, Berl., 1886, 2 : 301). Much later, Cantacuzene and Marie (*Compt. rend. Soc. de. biol.*, 1919, pp. 842, 981) showed

that *Vibriones choleræ* localized in the intestine after subcutaneous, intraperitoneal or intravenous inoculation. Sanarelli (*Ann. de l'Inst. Pasteur.,* Par., 1920, p. 870) confirmed this, so far as finding vibriones following intraperitoneal inoculation was concerned. Hahn (*Centralbl. f. Bakterol. u. Parisitenk. u. Infek.,* Jena, 1926, Vol. 81) says that Olsen and Ray found cholera vibriones in the intestine of guinea-pigs four hours after a subcutaneous injection. Masachi (*Ann. de l'Inst. Pasteur,* Par., 1922, p. 399) working in Besredka's laboratory, showed that cholera vibriones may be found in the intestine after intravenous, intraperitoneal or subcutaneous inoculation. The rabbit and the guinea-pig are refractory to the ingestion of large doses of living vibriones, but a definite intestinal lesion may be produced if living or dead vibriones are ingested after the previous administration of bile. Only the rabbits who have ingested living cultures after taking bile are immunized. The immunity acquired occurs without the participation of antibodies. Glotoff (*Compt. rend. Soc. de biol.,* 1923, 89 : 368) confirmed these facts, while Horowitz, Wlassowa and Perojnikowa (*Compt. rend. Soc. de biol.,* 1926, 99 : 1067), working in Russia, confirmed the above and showed that an immunity in guinea-pigs may be obtained by administering bile and feeding dead bacteria.

The wide occurrence of cholera in India has led a number of workers to attempt oral immunization against this disease.

An epidemic of cholera occurred at Pondicherry in 1925, which lasted about forty days. During this period there were 1039 cases and 831 deaths. Directly after the first cases were observed, 5200 individuals were immunized by the oral method. Of this group there were two deaths of the disease.

At Rajbari and the surrounding country, with a population of 6860 individuals, an epidemic of cholera occurred. There were forty-one cases and twenty-three deaths. Six hundred and ninety-three individuals were vaccinated *per os.* During the period of vaccination, forty-one new cases and seventeen deaths were reported. At the end of the epidemic, it was noted that none of the vaccinated group contracted the disease.

Lt. Col. A. H. Russell in a report to the League of Nations, *Health Organ,* 1927 ("Cholera Bilivaccine and Anticholera Vaccine—A Comparative Field Test") describes the results of an extensive comparative study between the value of subcutaneous cholera vaccination and oral immunization.

This work was begun in 1925 and completed in 1927. The cholera vaccines were only employed in villages where cholera actually occurred. There were 360 villages with a total population of 647,454. The subcutaneous vaccine was given alone in 236 villages, the oral vaccine was given alone in 52 villages, while both vaccines were given in 75 villages. In this group, the house was used as a unit; one-third of the inhabitants in each house received the subcutaneous inoculation, one-third were im-

munized orally, and one-third acted as controls. It should be noted that the inhabitants in these villages lived under identical conditions, as far as food, water and hygiene were concerned.

Results in Villages Where Oral Vaccination Was Practiced

	Cases of Cholera	Per Cent
4,982 vaccinated	18	0.36
11,004 non-vaccinated	222	2.02

Results in Villages Where Subcutaneous Vaccination Was Practiced

	Cases of Cholera	Per Cent
8,485 vaccinated	31	0.37
29,254 non-vaccinated	489	1.67

Villages Where Both Methods Were Employed

	Cases of Cholera	Per Cent
3,085 orally vaccinated	15	0.49
1,448 subcutaneous vaccinations	6	0.41
7,664 non-vaccinated	160	2.1

These results indicate that oral immunization in cholera is just as effective as the subcutaneous method.

Summary.—The above results show that it is possible to immunize against dysentery, typhoid and cholera *per os*. This method is particularly indicated for dysentery, because subcutaneous immunization is impossible, because of the severe local and general reaction following its use. For typhoid, oral immunization is possible and is perhaps as effective as the subcutaneous method. At all events, we have a method of immunizing patients suffering from tuberculosis, cardiac disease and kidney disease as well as pregnant women—conditions where subcutaneous inoculations are contra-indicated. Considering that oral immunization is just as effective as subcutaneous immunization in cholera, it should be the method of choice, because of the simplicity of administration, and the rapidity with which the immunity is produced.

Throughout this article, we have refrained from discussing the theory by which Besredka explains the mechanism of the infection and immunity in local immunity. We have simply stated the experimental facts and the practical applications based on these findings.

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CHAPTER VII

THE THERAPEUTIC VALUE OF LUMBAR PUNCTURE
AND OTHER METHODS OF APPROACH TO THE
CEREBROSPINAL FLUID SPACES

James B. Ayer

GENERAL CONSIDERATIONS

Lumbar puncture, first systematically carried out by Quincke in 1891, was recommended originally for the treatment of hydrocephalus. It often happens that the earliest use of a procedure may be the least important, and so it has been with lumbar puncture, for hydrocephalus was soon found not to be cured by repeated withdrawal of spinal fluid. Attention was soon directed to acute meningitis in which diagnostic studies and therapeutic effect of withdrawal of fluid proved of great value. But it is fair to say that the first fifteen years during which lumbar puncture was a new procedure were devoted chiefly to its use in diagnosis. Not until 1907 with the discovery of antimeningococcus serum was lumbar puncture given a status as a therapeutic method.

During the past twenty years lumbar puncture has been employed with increasing frequency, now the diagnostic and now the therapeutic value being stressed. Hardly a year passes without the publication of some new cerebrospinal fluid test or some therapeutic procedure concerned directly or indirectly with the ventriculosubarachnoid system. On the whole it must be admitted that to date the diagnostic advance has been more accurate, occasionally even dramatic (as in the use of lipiodol) than has the therapeutic. In fact, therapeutic procedures which seemed firmly intrenched, such as the use of salvarsanized serum, have been in part superseded.

The reason for this is seen in considering the anatomy and physiology of the fluid and fluid spaces. While much remains in doubt concerning both, it is unquestionably fair to consider the fluid as coming from the brain, by way of choroid plexuses for the most part and from the perivascular spaces of parenchymal vessels to a less extent, with general admixture by a process of to-and-fro motion, and not by any definite flow, but with tendency for the main stream to "set" away from the brain. Only under certain abnormal conditions (e.g., under the influence of hypertonic blood states) is there tendency to reabsorption by the brain tissue.

M. erector trunci

Spinous process of
    4th lumbar vertebra

Lig. flavum

Cornu coccygeum
    ossis sacri

Hiatus sacralis
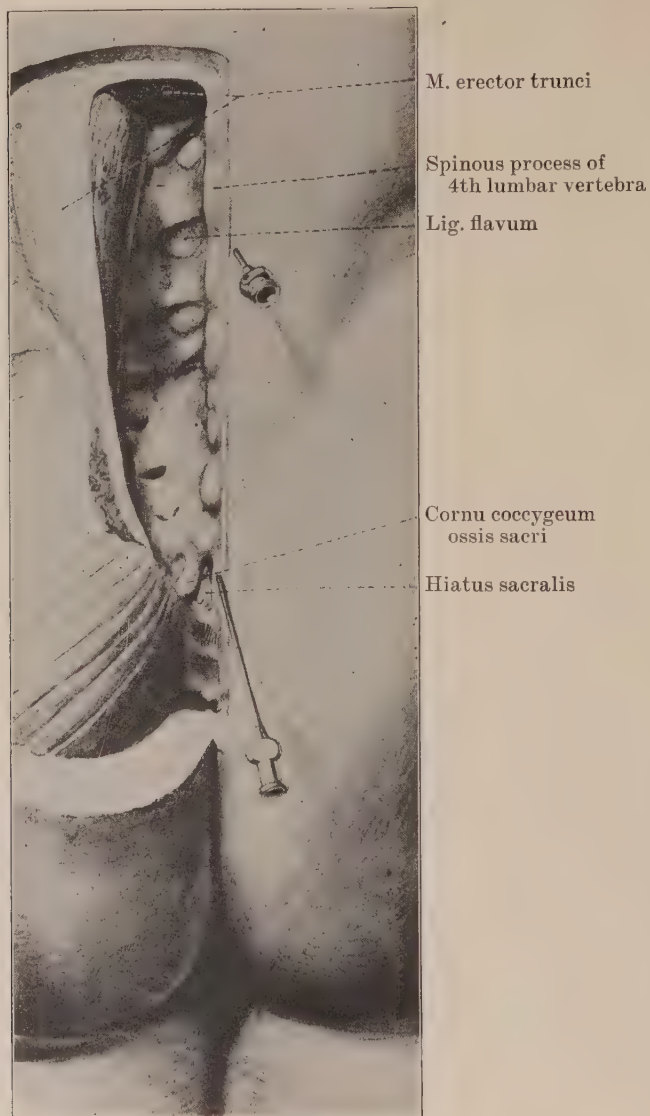
Fig. 1.—Topography of Lumbar Puncture.
The lower needle on the site of the extradural anesthesia. (From Tandler and Ranzi.)

Thus it is easy to understand pathological substances getting into the fluid from the brain for which appropriate tests may be devised, but difficult to imagine therapeutic agents going from the fluid into the brain. The fact that our points of entrance to the ventricles and subarachnoid spaces are so few is another drawback to successful therapy; and finally the plugging and damming of the fluid spaces at various points from
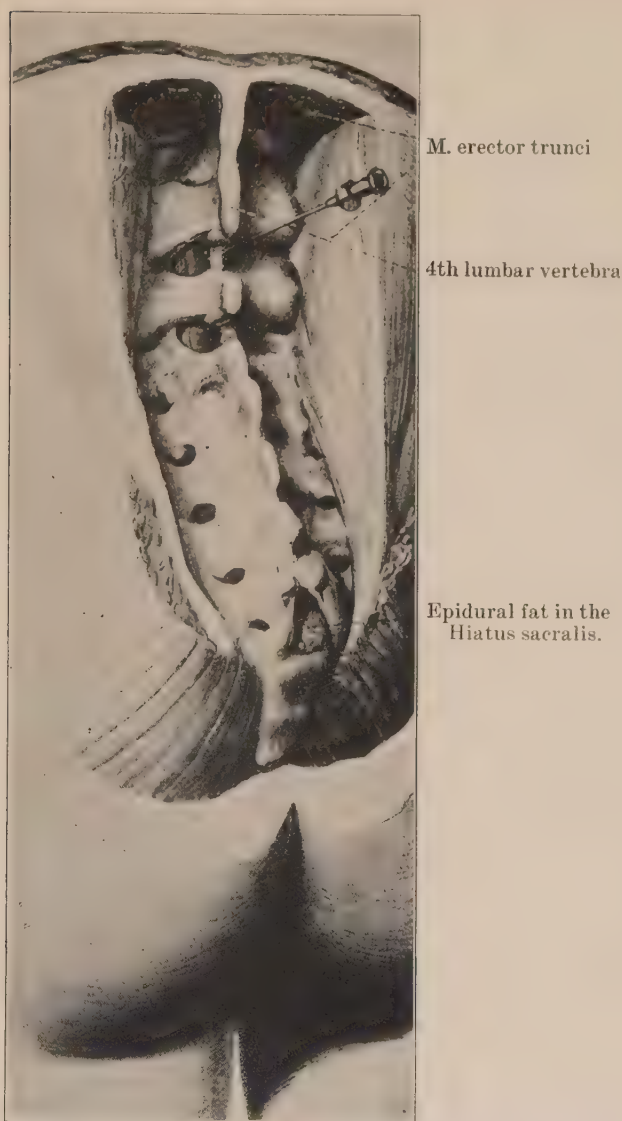
FIG. 2.—TOPOGRAPHY OF LUMBAR PUNCTURE. (From Tandler and Ranzi.)

inflammatory exudates render access to the fluid spaces incomplete or impossible.

It would, therefore, appear that therapy must be especially concerned with modification of pressure of the fluid, withdrawal of substances presumably harmful, and with the injection of medicaments designed to act upon the meninges, nerve roots or immediately adjacent nerve structure.
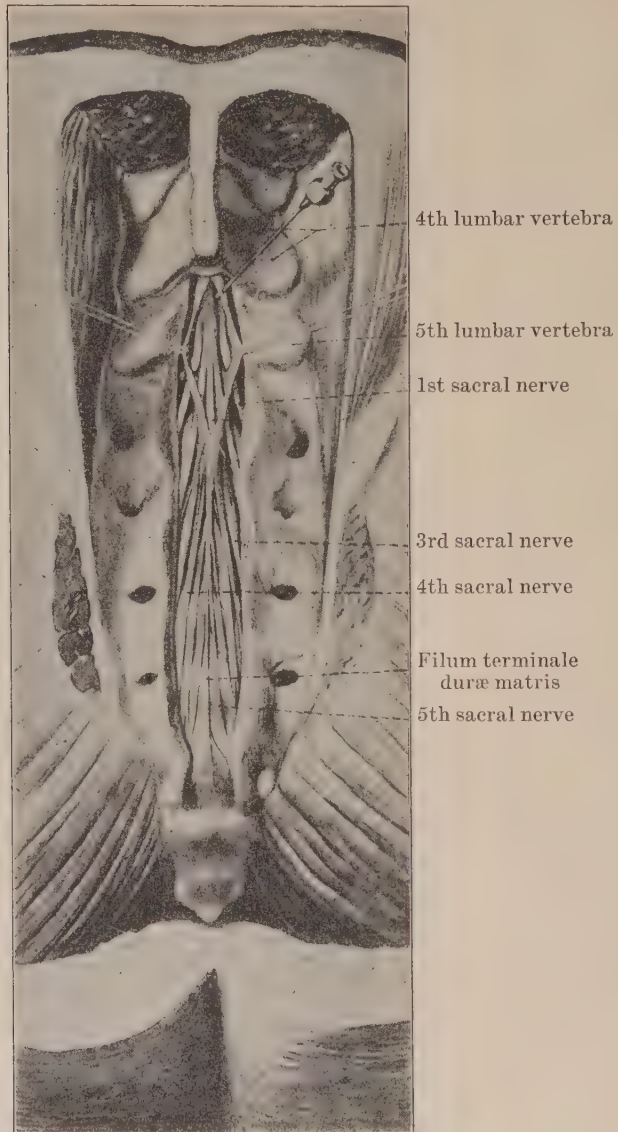
FIG. 3.—TOPOGRAPHY OF LUMBAR PUNCTURE. (From Tandler and Ranzi.)

Loci of Puncture

Clinical approach to the fluid pathways is usually through the classical lumbar puncture as originally described, but for special types of therapy two other well-recognized routes must be held in reserve, *i.e.,* cisternal (or suboccipital) puncture, giving approach directly to the cisterna magna, and ventricular puncture (or puncture of the corpus callosum), by which

the lateral ventricles may be tapped. Certain French writers describe dorsal and cervical punctures designed to reach the spinal subarachnoid space at various points, and Beriel gives the technic of transorbital puncture by which the chiasmal cistern may be reached; I can find no wide application of these more difficult and hazardous procedures, and doubt if they have been practiced in this country.

The apparatus employed in any of these methods is the same, with the exception of ventricular and callosal puncture, which are strictly surgical procedures and will not be detailed here.

The needle should be approximately 8 centimeters long and for most purposes of 18 gauge (for thick fluids 17 gauge is better). The writer prefers a nickeloid or platinum needle which will bend without breaking, but rustless steel needles are now on the market which render the objections to the old steel needle no longer tenable; most important, the needle should be fitted with a stylet which, when the needle is sharpened, should be flush with the point. This point must be sharp but short, *i.e.,* not too much beveled, so that when inserted the whole of the opening is within the fluid cavity. A three-way stopcock should be ready to fit the needle when the stylet is withdrawn, leaving one opening for withdrawal of fluid and injection purposes and a second for manometric measurements. Every well-conducted puncture demands pressure readings, and the simplest apparatus consists of two calibrated glass tubes of 1.5 millimeter bore, of a total height capable of measuring a column of spinal fluid of 750 millimeter. Some prefer a mercury manometer.[1] Where injection is planned, a small-bore rubber tube of 800 millimeter length, fitted with the bowl of a 30 c.c. glass syringe, is most satisfactory.

Technic of Lumbar Puncture

The technic of lumbar puncture may be briefly stated as follows: The patient should be placed on his side with head bent forward and knees drawn up so that the back is arched outward as much as possible. The entire lumbar field is now made sterile in any manner preferred. For point of puncture there are possible five interspaces, but that between the second and third lumbar vertebræ is usually the easiest, although individual variations make the use of another interspace sometimes better.

The skin is anesthetized by means of a fine needle with a little 2 per cent novocain, and it is good practice to carry the novocain 3 to 4 centimeters into the muscle along the track of subsequent puncture. This procedure usually prevents the patient from straightening the back when the larger lumbar puncture needle is inserted.

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[1] A mercury manometer is manufactured by Becton, Dickinson Co., Rutherford, N. J. A good aqueous manometer may be obtained from Codman and Shurtleff, 171 Massachusetts Ave., Boston.

Now, holding the thumb of the left hand firmly between the spines of the vertebræ selected, the lumbar puncture needle, with stylet held flush to the point, is introduced through the small opening already made, parallel to the axis of the spinal column, but tilted a little upward toward the head. After passing through the dense interspinous ligament, only slight resistance should be met until the needle passes the ligamentum flavum and then the dura, in adults usually at a depth of 5 to 6 centimeters.

Some prefer to avoid the interspinous ligament and commence the puncture 1 centimeter to one side of the mid-line. In such case the needle must be pointed inward a little as well as upward.

In case bone is encountered the needle should be withdrawn almost to the skin and a slightly different angle employed. If difficulty is again met, or if blood appears on removing the stylet (usually from the epidural venous plexus), another interspace should be tried.

Lumbar puncture in patients with meningitis and in some children is most difficult without a general anesthetic; especially if drainage and serum injection are contemplated is this to be recommended.

The accompanying drawings from the Atlas of Tandler and Ranzi (*Chirurgische Anatomie des Zentralnervensystems*, Berlin, 1920) give a good idea of the anatomical relations concerned in lumbar puncture.

Technic of Cisternal Puncture

The technic of cisternal puncture is copied from the paper of Wegeforth, Ayer and Essick: "The occipito-atlantoid ligament stretches from the posterior rim of the foramen magnum to the corresponding position on the first cervical vertebræ. Closely applied to its anterior surface is the dura mater and directly under this meninx lies that portion of the arachnoid membrane which forms part of the posterior wall of the cisterna cerebellomedullaris. The anterior wall of the cistern is formed by the posterior surfaces of the upper cervical cord and the lower part of the medulla. The depth of the fluid reservoir, namely, the distance between the arachnoid and the posterior surfaces of the cord and medulla, is about 1.5 centimeters at the level of the occipito-atlantoid ligament. For introducing the needle a point is selected in the midline of the back of the neck just above the spine of the axis. The glabella and the upper edge of the external auditory meatus were found to be valuable structures for directing the course of the needle, for a plane passed through them and the point of insertion on the back of the neck will pass also through the occipito-atlantoid ligament. This relationship has been a constant one in all of the subjects studied and is clearly shown in the illustration. In thin individuals palpation over the back of the neck often reveals a deep depression between the occipital protuberance and the spine

of the axis, and with the tip of the finger the approximate position of
the occipito-atlantoid ligament can be directly located. The distance neces-
sary to insert the needle in order to reach the cistern varies, of course, with
the individual. From a number of measurements taken at the time of
puncture on cadavers, the average distance was found to be 4 centimeters,
and it rarely exceeded 5 centimeters or was less than 3 centimeters. In
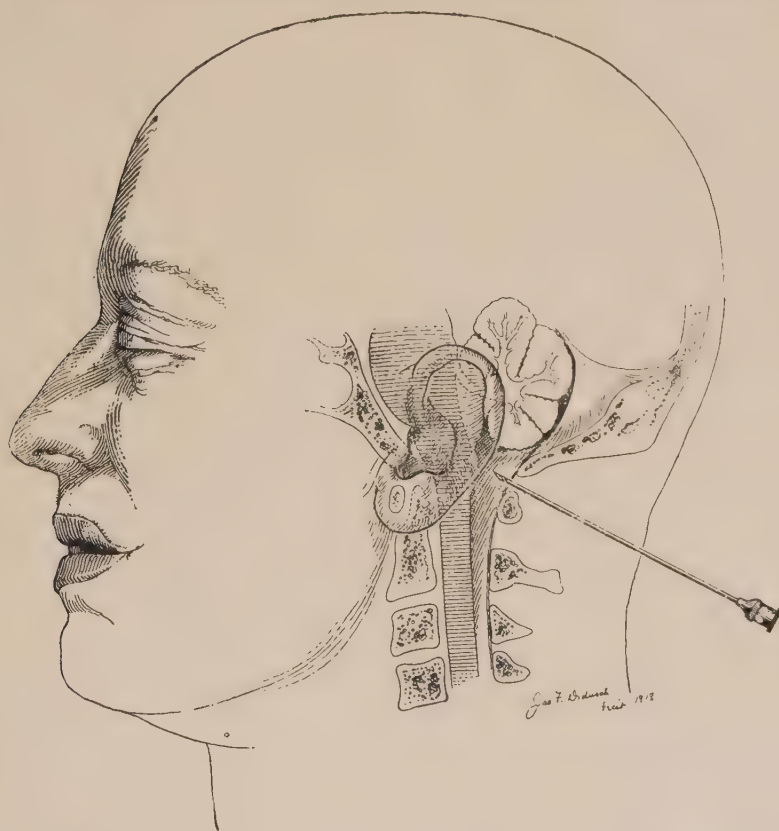
FIG. 4.—TOPOGRAPHICAL STUDY TO SHOW THE LANDMARKS USED IN PERFORMING CISTERN
PUNCTURE.

Composite prepared from numerous tracings of frozen sections. (From *Am. J.
M. Sc.*, Phila.)

view of the uncertainty occasioned by such measurement the operator
will find it necessary to rely upon his tactile impressions produced when
the point of the needle overcomes the resistance offered by the ligament
and dura and passes into the cavity of the cistern. For one skilled in
performing lumbar punctures this sensation is quite definite, and for us,
in performing the operation both in the clinic and at autopsy, it has
given an infallible index of when the cistern has been reached."

This description, written before the procedure had become common

on the living subject, cannot be improved. Cistern puncture is usually performed with the patient on the side with head gently flexed. Care should be exercised to prevent rotation of the head and thus dislocation of landmarks. In Germany this puncture is usually performed in the sitting position.

CLINICAL APPLICATION

The following brief summary gives in outline form therapeutic measures which have been employed, to which are added brief comments on each. In a given case more than one method of treatment via the spinal route may be employed, the indications for which will be discussed under the proper headings.

Methods of therapeusis include:

1. *Release of Fluid.*—This is designed to relieve pressure, or to rid the nervous system of poisons, toxins or waste products.

It is fair to state that almost every disease of the central nervous system has been so treated by somebody. On the whole, the successful results have been obtained in acute conditions; in certain headaches, in particular, striking amelioration of symptoms has occurred. Release of fluid is a method at once simple and usually safe and one worthy of trial to supplement other methods of treatment.

2. *A Release of Fluid with Introduction of Serum and Medicaments.* —Serum is unquestionably the most valuable of intraspinal methods of therapy.

B. *Medicaments.*—(*a*) ANTISEPTICS have been used in large numbers and in different dilutions, among them being lysol, carbolic acid, chloramin, flavin, potassium permanganate, corrosive sublimate, mercurochrome, gentian-violet, optochin, and salvarsan. Both in the experimental animal and in man, all of these antiseptics when employed in useful concentration have a marked irritative effect, and frequently lead to myelitis, encephalitis and respiratory paralysis. It is not too much to say that no antiseptic has yet been found which is both safe and effective.

(*b*) ANALGESICS have found a place in surgery. Novocain has been used many years and the newer methods of administration should be studied carefully.

(*c*) AIR is a relatively new agent, which may have a place in treatment of meningitis and certain headaches, especially the posttraumatic type.

3. *Combined Punctures for Purposes of Irrigation.*—By means of two or more needles at different loci, it is possible to irrigate the ventriculosubarachnoid space with Ringer's solution. Theoretically this should be a useful procedure, but in practice it is possible to wash out only a portion of the meninges, and it has not been shown to be as yet a highly successful method.

4. *Permanent Drainage.*—A method sometimes effective in meningitis; more often the needle, even though of large bore, becomes readily blocked. In theory a good method; in practice it is less effective than constant drainage established by surgical means as advocated by Haynes, Anton and Schmieden, and Dandy.

While many diseases may be benefited by lumbar puncture methods just described, the following may be considered especially amenable to this type of therapy:

Trauma to Brain.—In cerebral trauma, where death is not immediate, it is customary to find a very high spinal fluid pressure, due to bleeding and edema. Not infrequently death is imminent from respiratory paralysis. In such cases, marked benefit to respiration, pulse and consciousness may be brought about by simple release of fluid by lumbar puncture.

In mild cases, the withdrawal of fluid may in itself be curative; more often it is used to "tide over" the patient until he is in better condition for operation. In such conditions caution should be exercised in the amount of fluid taken, too much leading to further bleeding, too little being ineffective. Both Munroe and Jackson recommend withdrawal sufficient to halve the initial pressure and daily repetition of puncture until evidence of decrease of intracranial pressure is assured.

Posttraumatic headache and vertigo have in the past been most troublesome symptoms, yielding to no drug. Penfield has recently advocated the use of lumbar air injections in such states. He used in his seven cases amounts of air varying from 42 c.c. to 95 c.c.

Spontaneous Subarachnoid Hemorrhage.—This may be treated in the same manner if the intracranial pressure rises to a height likely to lead to death, or to control meningeal sequelæ. Neal speaks of lumbar puncture as "the most important measure in treatment," and Richardson had no ill effects from it. Symonds is cautious, relating the experience of another who had caused the rupture of an aneurysm in the lateral recess by withdrawal of fluid.

Lumbar puncture has of course been used in deep cerebral hemorrhage, but it is obvious that it can have little if any curative value.

Aseptic Meningitis and Serous Meningitis.—*Aseptic meningitis* occurs during the course of a number of febrile diseases, notably in pneumonia, and otitis in children. The fluid shows a cellular exudate without organisms and with normal sugar content; it is under increased pressure and is large in amount.

Serous meningitis, sometimes called Quincke's edema, is characterized by a large amount of clear fluid under increased pressure, but without cellular exudate. In some cases, the intracranial pressure is sufficient to cause choked disk of several diopters, thus leading to the name of "pseudotumor cerebri." The etiology of this condition is not clearly understood,

nor is an analogous condition called "hypertensive headache," in which the fluid pressure is also above normal.

From the therapeutic point of view these cases, the principal symptom of which is severe headache, may be successfully treated by withdrawal of spinal fluid and reduction of pressure. Sometimes one puncture is sufficient, more often repeated daily punctures are necessary.

There is a theoretical objection to lumbar puncture in septicemic states, as shown by Weed and coworkers who demonstrated that in animals with septicemia true bacterial meningitis may be precipitated by release of fluid. However, Wegeforth and Latham were able to find but five authentic cases where this had occurred in man, nor has the writer seen harm from this procedure.

Mention should also be made of the possible danger of medullary paralysis when fluid is released from below in all cases of excessive increase in intracranial pressure; this is unlikely in serous meningitis, but occasionally occurs in cases of brain tumor.

Acute Alcoholism (Ethyl and Methyl), Uremia and Carbon Monoxid Poisoning.—In these conditions, in which the fluid pressure is also high and the amount excessive, release of fluid has produced prompt amelioration of toxic symptoms, as testified to by many writers.

It is probable that in this group the good effects are attributable as much to removal of poisonous substances as to reduction of pressure, whereas in the previous groups mentioned, it is assumed that reduction of pressure is the desired objective.

In the above diseases and groups, amelioration of symptoms has been brought about by simple release of fluid. Two more conditions may be mentioned in which simple lumbar puncture has occasionally been of benefit. *Diabetes insipidus* may be temporarily controlled by this means but can hardly be said to be cured. *Labyrinthine vertigo* is another symptom which may yield to simple lumbar puncture. The writer has had two such cases in which lumbar drainage, *i.e.,* withdrawal of as much fluid as could be easily obtained, was promptly followed by cessation of vertigo. In neither case was the initial pressure of the fluid above normal.

We now turn to diseases treated by means other than simple fluid drainage.

Acute Poliomyelitis

It is now many years since Flexner and Amoss conclusively demonstrated that experimental poliomyelitis in monkeys could be prevented by previous injection of immune serum. Acting upon this experimental work, Peabody, Draper and Dochez employed human immune serum as a therapeutic agent in patients. Their results were not conclusive, yet at least two of these workers have continued to feel that immune serum given early in the disease is effective. However, Neal and Abramson's

report of the 1916 epidemic in New York is not encouraging as to the effect of this therapeutic agent and they quote similar unsuccessful results on the part of Netter in France.

In more recent epidemics human immune serum has been used more systematically and more intensively, with increasing faith in its value on the part of the workers. Wardner Ayer is enthusiastic concerning it and Aycock and Luther give statistics which, while not proof, are strongly suggestive of its potency. The method of administration as given by them is as follows:

Blood is drawn under aseptic conditions from the arm of a person who has recovered from poliomyelitis not less than a year before; this is allowed to clot, and the serum removed and kept in ampules. No preservative is used. They state that it will keep in the cold for six to eight months.

For injection they have used 15 to 20 c.c. of this serum intraspinally on two successive days, and 40 to 50 c.c. intravenously on the first day.

It is to be noted that serum apparently is effective only in the preparalytic stage of the disease, and therefore, because of uncertainty of early diagnosis, its applicability is limited to use in epidemics. Whether or not serum should be utilized as a prophylactic is a question of personal judgment.

In the clinically established case of poliomyelitis it is thought that frequent lumbar drainage is of value. It is not unreasonable to think that this is so, but there can be no proof that this is the case.

Neurosyphilis

One hesitates to describe a procedure which is certainly on the wane; yet the serum treatment of neurosyphilis is unquestionably efficient and is still the method of choice of some physicians in certain types of syphilis of the nervous system.

Shortly after the discovery of salvarsan it was found that the so-called parasyphilitic infections were influenced by intravenous therapy. Hoping to obtain even better results in these diseases, and especially tabes, salvarsan was injected directly into the spinal subarachnoid space. Severe reactions were obtained, among them destructive myelitis. Attention then turned to some method by which the good effects of salvarsan could be utilized safely, and salvarsanized serum was the result. In the United States the fundamental work was carried out by Swift and Ellis at the Rockefeller Institute, and the method adopted by them, sometimes with modifications, still stands as a simple and safe one. The technic, essentially as originally given, may be summarized as follows:

1. Intravenous injection of arsphenamin (0.3 to 0.6 gram) or neo-arsphenamin (0.45 to 0.9 gram).

2. In ½ hour 40 c.c. of blood is withdrawn and allowed to stand

over night in a large test-tube. The blood should clot and fall to the bottom of the tube leaving clear serum above.

3. Remove supernatant serum by means of pipet, taking no red corpuscles.

4. Heat to 56° C. for ½ hour.

5. Lumbar puncture and introduce 10 to 15 c.c. of the serum. More fluid should be removed than serum given, as intraspinal pressure will be increased by the aseptic meningitis produced by the serum.

The injections are commonly given once a week for six to eight weeks.

As has been said, certain modifications have been employed, especially that of Ogilvie in which serum is impregnated *in vitro* with known amounts—.0025 to .0050 gram of arsphenamin.

In the case of the Swift-Ellis technic, or that of Ogilvie, and especially in that of Byrnes, in which mercurialized serum is used instead of arsphenaminized serum, the reaction in *tabetics* is severe. Beginning about four to eight hours after the injection and lasting about twenty-four hours, pain is usually intense. The pain may be confined to the lower extremities, but may involve the trunk and arms also. There may be exaggeration of symptoms already in evidence, such as urinary incontinence and gastric crises; and there is also a systemic reaction, as evidenced by a slight rise in temperature. Following this the patient is unusually weak, but soon enters upon a period of greater comfort than usual.

In cisternal and ventricular injections, the routes of choice for syphilitic affections of the base of the brain and for general paresis, the reactions are less serious; pain may be slight or nil, but headache and vertigo may be troublesome.

Therapeutic results must be considered both as to the effect of serum upon the patient and upon the serology of the fluid. Again, therapeutic efficiency must be evaluated according to the type of neurosyphilis under treatment.

In *general paresis* it is probably fair to say that "cure" is seldom obtained, that "arrest" not infrequently results, and that "remissions" of a longer or shorter period are common under serum treatment. The clinical results published by numerous workers are much better than one would expect from the natural remissions occurring in paresis. From the laboratory point of view it is easy to obtain improvement in tests, but rarely does one obtain a normal spinal fluid even after several years of treatment. Sometimes when treatment has shown apparent clinical and laboratory success, Solomon has shown that the brains of paretics may show evidence that the pathological process is still active.

In *tabes* the successful reports are more numerous. Many cases are arrested and apparently remain so for years. One expects with confidence improvement in pain, in walking, in bladder symptoms and in oculomotor

symptoms. Crises, however, are frequently unmitigated, and optic atrophy and arthropathies are quite uninfluenced. Serologically the fluid often reverts to normal or shows only slight abnormality such as a residual weak goldsol curve.

Meningovascular syphilis, and especially the acute meningitic types, as a rule yield promptly to serum treatment, as judged clinically and from the laboratory tests.

With such good results as indicated above, why should serum treatment be losing favor at the present time? Because tabes and meningovascular syphilis yield also very well to intravenous therapy and because the results of serum treatment in paresis are as a rule not so good or so prompt as with tryparsamid or malarial therapy. Also, because the technic is tedious and painstaking, and consumes more time, both on the part of patient and physician, and the reactions, at least in the tabetic, are more severe than with intravenous therapy. In spite of these desiderata, serum treatment still holds a place in the obstinate case and sometimes success comes from its use when other methods fail.

Acute Meningitis

Unquestionably the most important therapeutic procedure in which puncture of the cerebrospinal fluid spaces is employed remains to-day, as it has been for twenty years, the serum treatment of meningococcal meningitis. If untreated or poorly treated this disease is usually fatal, or leaves residuals, such as blindness, deafness, paralysis and epilepsy. If properly treated the outcome is usually satisfactory, occasionally bordering on the miraculous. Success depends upon keen diagnostic ability and early and efficient treatment. A physician who undertakes to treat meningitis should be prepared to give unstinted time during the first week of illness and should early seek the help of bacteriologist, serologist, and if necessary, brain surgeon.

Confronted with a patient presenting meningeal symptoms, lumbar puncture should be made without loss of time, the physician having at hand *at this first puncture* culture-media proper for the growth of meningococcus (*e.g.,* blood agar) and at least 45 c.c. of antimeningococcus serum. If the fluid be turbid, the spinal canal should be drained, using jugular compression to obtain as much fluid as possible, usually as much as 60 c.c. in the adult. The serum should then be allowed to flow in slowly by gravity; if not hurried, 45 c.c. may be easily given, leaving the spinal fluid pressure less than that originally found. The foot of the bed should now be elevated to facilitate the flow of serum into the cranium.

It is good practice to give serum intravenously at this time, and this is especially recommended by Herrick in septicemic types of the disease.

Attention should next be directed to a study of the bacteriology of

the fluid. Meningococci may be easily found and recognized in a smear from this first fluid; more often a search at this time is fruitless or organisms of questionable type are found which puzzle the best of bacteriologists, and cultures seldom show growth under twenty hours. As soon as a positive culture has been obtained it should be typed, or better still tested against all available sera for its agglutination titer, so that the subsequent injections shall be made with the most potent serum obtainable.

During the time consumed in laboratory analysis and serum titration, usually not less than forty-eight hours, it is wise to assume that the organism present is the meningococcus, unless obviously otherwise, and that the sera at hand are potent, because in the first few days of the disease the fluid pathways are open for drainage and serum administration and the patient is in the best physical condition for drastic treatment. In the first two or three days, therefore, it is good practice to drain the spinal canal and inject serum at least twice daily. After this time, if the condition of the patient be favorable, once daily may be enough. After one week's treatment of this character, if cultures have become sterile, it is often wise to omit serum and observe the clinical condition, for serum is of itself an irritant and the aseptic meningitic reaction of the serum closely simulates that due to pathogenic bacteria. Favorable laboratory signs are clearing of the fluid, diminution and finally absence of organisms on culture, and progressive elevation of its sugar content. In the convalescent period occasional punctures are desirable to reduce pressure and carry away products of degeneration. Autovaccines are advocated at this stage by some.

Complications frequently occur. By far the commonest is inability to obtain more than a little fluid owing to collections of fibrinopurulent exudate in the canal. In such case puncture should be made at another place, usually higher, and it must be remembered that it is safe to puncture as high as the space between the twelfth thoracic and first lumbar vertebræ. Rotation of the head may also be employed to free exudate which accumulates in the upper cervical subarachnoid space. If in spite of these maneuvers a free flow is not obtained, the next step is to resort to cisternal puncture. It is sometimes most gratifying to obtain a large amount of thin cloudy fluid from the cisterna magna when the lumbar sac yields only a few centimeters of thick pus. Serum should then be applied by the cisterna route in the same manner as below, but with extra caution in warming it to body temperature. Occasionally at the end of a cisternal injection I have seen temporary cessation of breathing for a few moments, but always a return on artificial respiration. Undoubtedly patients have been saved by resort to cisternal serum therapy.

There are cases which do not yield even to cisternal administration of serum. In these ventricular puncture sometimes shows the organisms

in large numbers, and in washing out these reservoirs of infection the disease may be terminated. In this discussion of loci of puncture it may be said that our whole conception of meningitis may be wrong. According to Lewkowicz, the disease is primarily a ventriculitis and only secondarily meningitis. If such be the case we should theoretically attack the ventricle with our serum first and not last. While this may ultimately be found correct, I believe the course as outlined will usually be found effective and yet not too conservative.

Acute meningitis is not infrequently caused by pneumococci and streptococci, and more rarely by staphylococci, *B. influenzæ, B. pyocyaneous* and diphtheroid bacilli, etc. For all of these types of meningitis no potent serum exists. Attempts to use antiseptics of many kinds have as a rule proved futile and in some instances have seemed to hasten death. The writer has irrigated such cases with Ringer's solution from cisterna magna to lumbar sac and from ventricle to cisterna or lumbar sac, with success as judged by the amounts of pus washed out, but with no clinical benefit.

With our present knowledge it is probably safe to say that simple drainage of fluid is the best we can do in such cases. Under this treatment a very few cases of streptococcus and pneumococcus meningitis have been reported as having recovered, although in my experience all of these cases have proved fatal. Staphylococcus meningitis, however, is occasionally curable by this means.

Drainage may be carried out as already indicated, from lumbar or cisternal puncture once, twice and even three times in twenty-four hours or as often as signs of increased intracranial pressure appear. One writer reports recovery from pneumococcus meningitis after fifty such taps.

Constant drainage has been advocated by means of a retained lumbar puncture needle. This is reasonable in theory, but in practice I have found that the needle, even though a large one, blocks with pus and ceases to function; also the restlessness of such patients causes constant anxiety lest the needle be displaced or broken. For these reasons surgical drainage of the lumbar sac or more reasonably of the cisterna magna has been advocated.

Tuberculous meningitis in the experience of almost every physician is hopeless under any known form of treatment.

Spinal Anesthesia

While not exactly a method of treatment, anesthetization by lumbar puncture is assuming a position of importance in surgery. Used for a number of years, especially for low operations and particularly in prostatectomy, it has had some adherents and some who condemned it because of untoward effects. Recently the studies of Pitkin and McCormack appear

to have placed spinal anesthesia upon a more dependable and safer basis. This happy result depends upon the use of novocain so bound to a gliadin solution that rapid and undesired diffusion does not take place. By judicious change in the position of the patient anesthetization to almost any desired height may be safely accomplished.

In this manner so-called "controllable spinal anesthesia" has been found satisfactory for many operations, such as those upon the abdomen, for which this type of anesthesia was not previously considered safe or satisfactory. It has been especially recommended for obstetric practice.

Whether or not the new technic will prove useful in therapy in so-called medical conditions has not been proved.

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CHAPTER VIII

THE SUBSTITUTION OF TOXOID OR OF ANTITOXIN MADE IN THE GOAT OR SHEEP FOR ANTITOXIN MADE IN THE HORSE FOR PRODUCING TOXIN-ANTITOXIN

William H. Park

Some five years ago, Hooker pointed out that individuals after receiving toxin-antitoxin developed a certain amount of skin hypersensitiveness, the material used by him being a number of medical students. They were first given an intracutaneous injection of 0.1 c.c. of a 1 : 100 dilution of horse serum. They were then given three doses of the old preparation of toxin-antitoxin which contained thirty times as much horse serum as the present 1/10 L plus preparation. At the end of a year the students showed considerably more reactions from the intracutaneous test than they did at the time of beginning the investigation. It should be noted that these students received at least forty times as much horse serum as those receiving immunizing injections of the new preparation of toxin-antitoxin.

In some work carried out by Schroder and myself, we corroborated the work of Hooker, except that we found with the new preparation a smaller increase in the number of children reacting. Our tests were made in a somewhat different way from Hooker's in that we tested one hundred children who had received toxin-antitoxin and used new children of the same ages for the control test. The reactions were increased somewhat in number but not appreciably in size. Since then I have had the opportunity of witnessing the results of giving scarlet fever antitoxin to the children in two institutions caring for children. In each of these, about 30 per cent had had toxin-antitoxin while 70 per cent had not. The reactions were practically the same in both series of children.

There is a tendency to attribute to a previous injection of toxin-antitoxin bad results which follow the use of antitoxin later. Certainly at times this is not a fair assumption. For instance, a case of gangrene at the point of injection of a subcutaneous dose was attributed to toxin-antitoxin given a year before, while the facts as stated in the journal showed that the patient had received an injection of diphtheria antitoxin ten days before the dose was given, which was followed by immediate swelling of the local tissues and later gangrene. There can be no doubt that this condition was produced by the first injection of serum given ten days before. The fact that no reaction happened within a few days of the first injection

clearly eliminates the toxin-antitoxin from having produced a sensitization which produced this lesion. Whether or not injections of the new prepara-ration of toxin-antitoxin with its greatly lessened amount of horse serum sometimes increase the tendency of persons already sensitive to react to a therapeutic dose of horse serum is a debatable question. Even if it does not there is no disadvantage in our substituting antitoxin made either in goats or sheep for that made in the horse. The goat and the sheep are far enough removed from the horse to make it practically impossible that the small amount of serum used would have any effect in sensitizing to horse serum.

Toxoid, which is made by adding formalin to toxin to the extent of 0.2 per cent and leaving in the incubator for one month to six weeks, is also a perfectly efficient preparation. Both toxin-antitoxin and toxoid should be made from strong toxins and should be standardized for potency in guinea-pigs before being distributed. Both preparations give practically the same results of from 75 to 95 per cent efficiency, according to the potency of the material and the ages of the children, the younger children giving a somewhat greater percentage of immunity than the older ones. The toxin-antitoxin, because it is made from greatly diluted toxic broth, gives less reaction in older children.

The French use a preparation called "anatoxin" which is prepared by leaving it in the incubator for a long enough time to practically eliminate all toxicity. When it is properly made, it is a thoroughly potent product. This preparation is also excellent and gives even less reaction than the toxoid in infants and young children. Both forms of toxoid have about thirty times as much of the soluble substance of the bacilli and the broth materials as the toxin-antitoxin. It is for this reason that they give more marked reactions in the older children and adults. It is probable that within a very short time all biological plants will be distributing toxin-antitoxin made from goat or sheep antitoxin, or a toxoid or anatoxin.

It is certainly very important to eliminate any worry as to the possi-bilities of sensitizing to horse serum, otherwise physicians will be afraid to give the toxin-antitoxin or to give antitoxic or antibacterial sera later, as these therapeutic sera are necessarily made in the horse.

CHAPTER IX

TREATMENT OF CHRONIC EPIDEMIC ENCEPHALITIS

Hubert S. Howe

Consideration of the treatment of any chronic disease comprises the specific treatment of the disorder and also the measures which alleviate the most distressing symptoms. Unfortunately, for chronic epidemic encephalitis we have no specific treatment, and most of the remedies advocated have given but indifferent results.

Protein therapy has been well recommended. For this purpose milk, aolan, leukocytic extracts and vaccines have had the greatest popularity. Milk is advantageous in that it is easily available and its preparation is simple. Fresh or pasteurized milk is boiled for from five to ten minutes and, when cool, 5 or 10 c.c. are injected intramuscularly. Aolan is a preparation of casein which may be obtained in ampules and is a more chemically constant product. One-half to one cubic centimeter of this solution is administered intravenously. Injections are followed in about an hour by a sharp chill and accompanied by malaise, headache and a moderate rise in temperature. Of the vaccines, typhoid has been the most commonly employed. Twenty-five to fifty million organisms are given intravenously for the first dose, and if the reaction is not too great, the dose may be increased to one hundred million. This treatment is quickly followed by a chill and high temperature reaction. Further doses may be given in a few days or at weekly intervals. My personal experience with protein therapy has not resulted in definite benefit. I have observed many patients who have had this treatment and but few who were at all enthusiastic about its results.

Malaria inoculation has been tried in a limited number of instances but the results have so far not been particularly encouraging.

Benefit has been obtained by the long-continued use of hypertonic solutions intravenously. Many writers have found hypertonic solutions of dextrose useful and, in over six years' experience with it, I believe that it is the most valuable measure advocated to date. Two hundred cubic centimeters of a 25 to 35 per cent solution are given at intervals of three to seven days.

The intravenous administration of sodium iodid solutions has been advocated by Farnell.[1] He uses 100 c.c. of a 10 to 25 per cent solution at

[1] F. J. Farnell. "Extra-Pyramidal Tract Disease with Special Relation to Epidemic Encephalitis." *Medical Society Reporter*, March, 1928, Vol. 22.

weekly intervals, and believes that with this treatment he obtains not only the effect of a hypertonic solution but also a valuable specific effect on the virus of encephalitis.

The majority of patients who present themselves for treatment have either paralysis agitans, mental and behavior disorders, alterations of sleep or respiratory disturbances. The paralysis agitans syndrome is by far the most usual form of chronic epidemic encephalitis. While the course of this form of the disease is usually progressive, it is by no means always so, and it may become stationary or gradually improve. This uncertain course of the disease makes it very difficult to evaluate the effect of any form of treatment. The specific symptoms for which relief is sought are, chiefly, tremor, rigidity, weakness, pain and the inability to perform certain movements or to accomplish more complicated acts, such as turning in bed, getting out of a chair, dressing, etc. The tremor is usually the first symptom that calls the patient's attention to this insidious malady. The slowing of motor activity, suppression of automatic and associated movements and the mechanicalization of attitude and motion often creep on so slowly that the patient does not notice them until the condition is fairly well advanced. For the symptomatic treatment of paralysis agitans, the alkaloids of the belladonna group are invaluable. Small doses of hyoscin hydrobromid and atropin sulphate, separately or in combination, should be given at the outset. As some individuals have an idiosyncrasy to these drugs while others are affected by very small doses, 1/200 grain of either hyoscin hydrobromid or atropin sulphate, if given singly, or 1/300 grain of each, if used in combination, three or four times daily, is prescribed. The effect of the drugs on the pulse, pupils and secretions should be carefully observed and the dose gradually increased until the maximum benefit is obtained. In most instances, a combination of these alkaloids in about equal dosage is superior to either individually. Hyoscin has a decidedly sedative effect, while moderate doses of atropin are excitant. Hyoscin, if used alone in sufficient doses to produce a satisfactory therapeutic result, may produce excessive fatigue and drowsiness. This may be overcome by the use of atropin, or by the addition of one or two grains of caffein citrate. Atropin is more cycloplegic, causes more suppression of mucous secretion, and has more pronounced effect on the vagus endings in the heart than hyoscin. If the dryness of the mouth is excessive, it may be relieved to some extent by the addition of pilocarpin nitrate, in doses of 1/10 to 1/4 grain. There is some acquired tolerance to these alkaloids and, if the doses are increased slowly, many patients will tolerate 1/60 grain each of atropin sulphate and hyoscin hydrobromid for long periods. In individuals under fifty, they may be continued without intermission for months or years, but in patients above this age, neither atropin nor hyoscin in doses sufficient to produce much alleviation to the rigidity or tremor may be well tolerated. Elderly patients may complain

of dizziness, headache, confusion and loss of memory, so that the administration has to be frequently interrupted or discontinued. Hyoscin and atropin, however, should be given a thorough trial in all patients with the paralysis agitans syndrome as, if properly employed, their action is useful in the majority of instances. Occasionally, very minute doses, 1/800 grain, are of benefit, especially if administered hypodermatically.

Until recently, the use of the belladonna alkaloids in paralysis agitans has been considered entirely palliative. However, in following many patients in whom this syndrome has been caused by epidemic encephalitis, where this medication has been continued for months or years, definite improvement is at times observed.

The tremor may be alleviated, if it is mainly confined to one arm, by carrying a heavy stick or other article in the affected hand. Some men conceal and restrict the activity to some extent by keeping the hand in a coat pocket. In some instances where the tremor is very persistent, patients have found relief in applying a molded splint to the forearm and bandaging it firmly in place. This can be worn for several hours and will help to relieve the pain and fatigue which may be caused by a persistent tremor. This device has also been found useful when a severe tremor keeps the patient from going to sleep promptly. Passive movement also inhibits a tremor, and a limb may be rested by an attendant constantly moving the affected part or in attaching it to some mechanical device which accomplishes the same purpose. Before retiring, a neutral bath is the most valuable of hydrotherapeutic procedures, and should be continued for at least twenty to thirty minutes. It will be found relaxing and also alleviating to the tremor. It has been my experience that the rigidity has been more relieved by belladonna than the tremor. Other methods for the alleviation of the rigidity are massage and hydrotherapy. For the pains resulting from the constant muscle tension, there is nothing as beneficial as massage. It should be combined with vigorous passive movement in an attempt to overcome the tendency to overaction of the flexor muscles and the stiffness of the joints.

The inability to perform certain complicated movements, such as getting up and out of a chair, turning over in bed, etc., can be remedied by reducing them to a number of simple movements to be performed in rotation. For instance, in getting out of a chair, the feet are brought back as far as possible underneath the chair, the patient then leans forward until the center of gravity is over the feet, then the legs are extended and the patient rises to the standing position. There may be some inhibition in starting to walk and, if so, he may count one, two, three, and train himself to start forward with the right or left foot on the count of three.

Mental and behavior disorders are difficult to treat and, in general, are to be cared for as an organic psychosis. The distressing character changes seen in childhood and adolescence need isolation and protection.

Correction and training are necessary but must never be carried out with severity or corporal punishment. A regular routine with constant kindly supervision will in the end frequently lead to recovery. Physical over-exertion and undue excitement are to be avoided as in all forms of this disease.

The most frequently encountered mental disorder in adults is an apathy which varies in different individuals from a simple laziness and inability to do anything without effort to a lethargy which makes the necessary activities of life a burden and any further exertion an impossibility. This is an exceedingly difficult symptom to modify or relieve in any way. It is extraordinarily persistent and may remain after most other symptoms have passed away. It may be relieved temporarily, to a certain extent, by the administration of caffein citrate, in doses of one to three grains, three times daily. One sees an occasional patient who complains only of nocturnal wakefulness and diurnal drowsiness. The inability to stay awake in the daytime may be the detriment to working. Suitable doses of amytal at night and caffein citrate in the day may enable him to continue his occupation.

The respiratory disorders which call for treatment in chronic epidemic encephalitis are recurring attacks of tachypnea. These attacks of gasping respiration are fortunately not very frequently encountered and they usually cease spontaneously, after years or months of troublesome persistence. Sedatives should be given a trial in all instances, but they will usually be found ineffectual. Luminal and bromids have been advocated, but they have to be given in fairly large doses.

THE CALMETTE-GUÉRIN METHOD (B-C-G) OF VACCINATION AGAINST TUBERCULOSIS

George H. Smith

While the nature of the mechanisms involved in the development of an immunity spontaneously acquired to an infectious agent is far from clear, it is obvious that all of the phenomena contributory to that immunity are based upon reactions induced either directly or indirectly in the host by the state of parasitism. To the parasite or to its metabolic or disintegrative products the host responds with the elaboration of a new defensive mechanism or with the enhancement and activation of a mechanism originally and naturally present. Although in specific instances there appear to be exceptions to the rule, it seems that within clearly defined limits the defensive response is proportionate to the stimulus applied.

In so far as can be determined at present, there is no reason for believing that the basic principles involved in the establishment of an artificial acquired immunity are other than those exhibited in spontaneous immunity. At all events those immunizing procedures which have proved most efficient have been based upon methods which closely simulate processes of spontaneous infection. Experience indicates that any method of immunization designed to relieve the host from the stimulation provided by the action of the parasite is of relatively incomplete effectiveness, whereas those procedures, such as the establishment of a vaccinia, which force the defensive mechanisms to become operative lead to a more efficient and durable immunity. The problem of prophylactic immunization involves, then, the adoption of a procedure which simulates to the closest degree those actions and reactions characteristic of spontaneous infection, with the limitation that the method employed must be subject to control.

In these respects tuberculosis and tuberculosis immunity offer no exceptions. It has long been believed, and there is much evidence to support the idea, that the most effective means of inducing a resistance to parasitism by *B. tuberculosis* is that provided by the changes induced in the body through a previous implantation of tubercle bacilli. Consequently, for several decades much effort has been expended to the end of discovering some agent, in itself harmless, possessing the stimulating attributes of viable, virulent tubercle bacilli.

It is only necessary to recall a few of the studies made during this

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period to indicate how consistently this basic principle has been kept in mind, even though in most other infectious diseases prophylactic studies have followed other directions. The extent and the diversity in methods of attack are recalled by mentioning such studies as those of Behring, Roemer, and Ruppell, in 1902; of Koch and Schütz, of Neufeld and Miessner, in 1905, and of Klimmer, in 1908, in all of which bovine tubercle bacilli were used. In 1906, Arloing conducted similar investigations with human bacilli, as did Webb and Williams, in 1909. Attempts were made to use avian bacilli by MacFadyean and his associates, in 1913, and ichthyic bacilli have been employed more or less continuously from the time of Friedmann, in 1903, to the work of Kolle and Schlossberger, in 1920. More recent studies, still based upon this same concept, are those of Vallée, in 1924, who attempted to effect a retardation in the absorption of virulent organisms; those of Shiga and his associates, who sought to obtain an attenuated tubercle bacillus by suppressing virulence through growth of the organisms in media containing various chemicals, and those of Ferran, who attempted to immunize with his "Alpha" bacterium, an organism which he regarded as a non-virulent mutant of *B. tuberculosis*.

None of these attempts has, however, fully met the essential conditions. While in many instances the procedure has been attended by the development of an immunity of some degree, the increased resistance has been too slight or too transitory to be of practical importance. In other instances the immunizing agent itself has been of so uncertain a character as to its harmlessness that an extended use, under conditions which could not be carefully controlled, was unwarranted.

The most recent and, as it would seem, the most effective agent thus far devised for prophylactic immunization against tuberculosis is the so-called "B-C-G" of Calmette and Guérin.

This product, "bacille bilié Calmette-Guérin," is prepared from a virulent strain of tubercle bacilli of the bovine type. During a series of some 230 successive cultivations extending over a period of thirteen years, the virulence of this organism has become markedly attenuated, and it appears to have become established in a more or less stable state as regards its invasiveness. Throughout the entire period of artificial cultivation, but a single culture-medium was used, namely, potato impregnated with beef bile containing 5 per cent of glycerol. Through its growth on this medium certain new characteristics have become established, but the organism has not lost its inherent character as a tubercle bacillus and retains its capacity to produce tuberculin. Cultures that have been held upon the bile medium for an indefinite period may be returned to ordinary media suited to the growth of tubercle bacilli without reverting, at least quickly, to the original virulent type.

In the experimental animal most certainly, and a somewhat limited experience indicates that comparable reactions occur in man, growth of

the modified organisms in the body leads to the development of reactions possessing many of the characteristics of localized pyogenic infections. These localized changes, which may be observed in animals that have been inoculated for a period of but three or four weeks, regress and after a period of three months or more no anatomical evidences of infection are to be found. Apparently similar reactions take place in children inoculated with the B-C-G vaccine. There is a quite general agreement to the effect that the bacilli retain virulence to a slight degree, but that there is a marked tendency to localization with subsequent healing.

In so far as can be determined upon the basis of chemical analyses, cultivation of the organisms in the modified environment leads to no very profound changes, particularly as regards their content in fatty acids, waxes and lipoids. The staining characteristics, *i.e.,* the acid-fastness, of the organism remains unchanged as does the morphology of the single cell. When stained by special methods, however, such as the silver impregnation procedure, the B-C-G bacilli resemble in many respects tubercle bacilli of the human type. It would appear that the ectoplasmic membrane of the B-C-G organisms is definitely thinner than is that of ordinary and virulent organisms.

From the standpoint of toxicity referable to the bacterial protoplasm itself it would seem that the B-C-G organisms, like many other bovine and human strains that have been deprived of virulence, retain their toxic properties and in this respect may be differentiated in no way from highly virulent organisms. The retention of toxicity may be demonstrated not only in tuberculous animals but in those which are normal.

As stated above, B-C-G retains its capacity to produce tuberculin, and the tuberculin so elaborated is comparable in activity with that produced by other strains of *B. tuberculosis*. This again indicates a lack of parallelism between tuberculin production and the virulence of an organism. Not only do the organisms retain their power to produce tuberculin *in vitro,* but when injected into normal guinea-pigs, and this is true also of injections into human beings, the vaccine may induce a state of tuberculin sensitivity. This does not necessarily prove, or even imply, that hypersensitiveness to tuberculin and immunity to tuberculosis are due to but a single mechanism, although unquestionably both states can be induced not only by virulent tubercle bacilli but by those which have lost their virulence, such as B-C-G.

Along with a retention of tuberculogenic action, the B-C-G organisms retain their power of functioning as antigens, and antibodies, in particular those responsible for the complement-fixation reaction, may be developed with B-C-G just as with normal, virulent or non-virulent tubercle bacilli. The antibodies so produced appear to be qualitatively the same as those artificially produced with other strains of tubercle bacilli or those evolved during infection.

In the preparation of vaccines designed for use in immunizing against tuberculosis, organisms of the B-C-G type are grown in fluid media. Flasks of the synthetic medium of Sauton are inoculated with the stock strain of B-C-G organisms; growth occurs rather rapidly and abundantly and by the end of the fourth week the bacilli recovered from such a flask, containing 1,000 c.c. of medium, weigh somewhat more than 5 grams. The vaccine is prepared by collecting these organisms upon a sterile filter paper. They are then pressed between layers of filter paper until they are largely free of fluid. The partially dried organisms are transferred to a sterile platinum dish and are weighed. Each centigram of the weighed culture contains about 400 million bacilli. The dried and weighed organisms are transferred to a sterile flask and after the appropriate amount of dilution fluid is added they are shaken vigorously with glass beads in order to procure an homogeneous suspension. The fluid employed for dilutions of the vaccine consists of 40 grams of glycerol and 10 grams of glucose to each liter of distilled water. With this solution the suspension of organisms is diluted until each 2 c.c. of the preparation contains 1 centigram of bacilli. Organisms suspended in this fluid remain viable for but a relatively short time, the period depending upon the temperature and upon other factors, such as exposure to light, which in general influence bacterial viability. When held in the icebox, however, at a temperature not higher than 5° C., the viability of the organisms is definitely increased. In view of the fact that for its efficiency it is requisite that the organisms of the vaccine be living, no vaccine should be employed which has been prepared for more than ten days.

For the administration of B-C-G vaccine two routes are available, the digestive tract and subcutaneous injection. The method of choice depends upon the conditions governing the work, the determining factor being more particularly the age of the individual, although there can be no question that the enteral route is more efficient than is subcutaneous inoculation. The selection of the gastro-intestinal route is based upon the observation that in the newborn the mucous membranes of the enteric tract are far more permeable, not only for soluble principles, such as bacterial toxins, but for bacterial cells themselves, than are the membranes in later life. A second very important factor is the observation that in the newborn, and this applies not only to human beings but to laboratory and domestic animals as well, there is a far more marked tendency for organisms which pass the intestinal mucosa to become localized in neighboring glandular structures. In the adult, or even in the adolescent, intestinal permeability is reduced to such an extent that it is essentially negligible and the tendency for a more general distribution of organisms is more outspoken. This period of extreme permeability appears to persist for not longer than the first ten days after birth. This fact arbitrarily limits the time during which enteral vaccination is effective to its highest degree.

In administering B-C-G by mouth the procedure adopted as a routine method consists in giving to the newborn infant three successive and equal doses of living B-C-G culture at forty-eight-hour intervals. These can be given on the third, fifth and seventh days after birth, or on the fourth, sixth, and eighth days, or even upon the fifth, seventh, and ninth days. Each dose consists of 1 centigram of bacilli in about 2 c.c. of fluid. This represents approximately 400 million bacilli. For the administration each dose is added to a small quantity of milk at body-temperature and is given to the infant about one half hour before feeding. Such administrations lead to no disturbance of any kind.

The second mode of administration, that is, injection by the subcutaneous route, appears to be somewhat less effective and, indeed, unless some care is taken in regulating dosage, reactions of greater or less importance may ensue. Prophylactic treatment by this route may be resorted to in the case of older infants and even in adults who are clinically free of tuberculosis and who give consistently negative tuberculin reactions. In this mode of treatment but one subcutaneous injection is given and the quantity injected should be reduced to such a point that the formation of a cold abscess will not ensue. In children the dose should be no greater than $\frac{1}{15}$ of a milligram; that is, about six million bacilli. In adults, a larger quantity, 1 milligram, may be employed. Persons with a temporary tuberculin anergy should not be injected with the vaccine, since in such individuals quantities as small as 0.2 milligram have elicited a typical Koch phenomenon.

The efficiency of B-C-G as an immunizing agent may be determined upon the basis of the mortality rates, due consideration being given to the environmental conditions under which the vaccinated and non-vaccinated children dwell, or upon the basis of the effect of the immunization upon tuberculin reactions. This latter method of evaluating the procedure is less reliable than is the method determined by the relative death rates. Despite much evidence to the contrary, it would appear that sensitivity to tuberculin is not a necessary condition to immunity, since the latter is to be obtained only when the lymphatic tissues of an individual are parasitized and it makes no difference whether the parasitic organism is or is not endowed with virulence.

The relationship between B-C-G immunization and the development of positive tuberculin reactions may be indicated by a tabulation of the results in two groups of vaccinated children as presented by Calmette. One group of these children lived in an environment which was free of obvious opportunities for spontaneous infection. The other group dwelt in an environment where the opportunity for infection was abundant.

These figures show, and further studies have given results of the same character, that the administration of B-C-G renders about 25 per cent of infants living in a non-infected environment susceptible to tuberculin

Vaccinated Children Living in a Contaminated Environment

Age	Number of Children Examined	Positive Cutaneous Reactions	Average Weight in Grams	Per Cent Showing Positive Reactions
3 months................	54	6	4195	11.1
6 months................	48	8	6730	16.6
9 months................	27	7	8120	25.9
12 months................	15	4	4690	26.6
15 months................	9	4	11,000	44.4
18 months................	10	5	11,450	50.
24 months................	5	3	12,280	60.

Vaccinated Children Living in an Apparently Non-infectious Environment

3 months................	119	5	.....	2.5
6 months................	169	7	.....	4.1
9 months................	119	7	.....	5.8
12 months................	78	6	.....	7.6
15 months................	65	5	10,920	7.4
18 months................	39	5	11,930	12.9
21 months................	20	4	12,300	20.
24 months................	14	4	12,900	28.

at about the end of their second year. In the infants of the other group this proportion eliciting a positive tuberculin test is attained at the age of nine months. This in itself indicates that the superimposed infection with virulent organisms is responsible for the much higher percentage showing positive tuberculin tests, and at the same time because of this added infection it indicates that the protective action of the vaccine is very considerable. A fact which should be taken into consideration in attempting to interpret these figures is the observation that frequently vaccinated children will manifest a positive tuberculin test for a few weeks or even a few months at some time after vaccination and then the reaction becomes negative. It would thus seem that while B-C-G administration may exert some effect upon the development of tuberculin sensitivity the later phenomenon cannot be taken as a measure of the efficacy of the vaccine.

A determination of the efficiency of B-C-G vaccination based upon the death rate is also very difficult to accomplish, since many factors contribute to render a statistical study of somewhat questionable value. On the other hand, if we may disregard these contributory factors and assume that within certain limits these disturbing features tend to neutralize each other, an approximate index of efficiency may be obtained. It appears to be well established that in France the infant mortality from tuberculosis reaches at least 24 per cent in the case of children born or raised in

families where familial contagion is possible. In the opinion of all observers this figure has been greatly reduced by vaccination. Thus, since 1924, there were 52,772 infants treated with B-C-G in Paris. Of this number, 5,749 had mothers who were tuberculous. In one group of vaccinated children who were observed up to the age of one year, the general mortality amounted to 3.1 per cent, and the mortality from tuberculosis was 0.9 per cent. Similar figures have been obtained in other localities; for example, in Barcelona, where the death rate from tuberculosis in 200 vaccinated children amounted to 6.18 per cent, while in the uninoculated a death rate of 23 per cent was obtained. Similar results upon smaller groups of cases, not only in France but in many other countries, have been reported.

These results clearly indicate that under certain conditions the use of B-C-G as a prophylactic agent in the control of tuberculosis is effective. Naturally, since the work in children has been carried on only since 1921 and, indeed, the major part of it has been done since 1924, it is somewhat premature to pass judgment upon the ultimate effects of the treatment. The probable duration of the immunity established is not known with any certainty, although apparently in most instances the immunity conferred persists throughout that period of life when the greatest danger of infection and most serious consequences of infection exist. It would seem that for a period of four years at least, protection, in the absence of frequent and massive infection with virulent organisms, is adequate; it may very well be that during later childhood a spontaneous immunity may have become established.

Naturally the use of vaccination of this type has far greater possibilities in countries where tuberculosis is very prevalent and where the opportunity for infection very early in life is abundant than in countries where such infection does not exist to a like degree. The use of B-C-G vaccine in relatively non-infected countries may well be of questionable expediency. This is due solely to the fact that the evidence at present available does not with any assurance guarantee that the attenuated organisms used in the vaccine may not, under suitable circumstances, regain virulence.

Naturally in localities with a high tuberculosis infant mortality, this danger is not to be compared with the almost certain chance of infection and the relative degree of protection obtained more than outweighs the danger of conferring infection in isolated instances by the vaccine. Calmette and his associates are convinced that when properly maintained under artificial conditions, the B-C-G organism does not revert to a virulent type. On the other hand, it has been unquestionably shown that under other experimental circumstances virulent tubercle bacilli may be derived from the attenuated bovine culture. This being true, it is probable that the general use of the vaccine should be limited to those districts in

which the dangers of spontaneous infection far outweigh the danger of a possible infection associated with the administration of the vaccine. And here, in these regions of greatest usefulness, B-C-G vaccination seems to have produced results far superior to any procedure hitherto devised.

CHAPTER XI

THE PRESENT STATUS OF VACCINATION IN TUBERCULOSIS

Lawrason Brown and Fred H. Heise

GENERAL CONSIDERATIONS

Clinical observation establishes the fact that infection with the tubercle bacillus and the development of a focus of disease does not result in complete protection against subsequent infection and disease. Nevertheless, those races of people living in crowded or urban regions and exposed to the tubercle bacillus for ages do not as often develop tuberculosis in the rapidly fatal forms as do those in whom the tubercle bacillus is a recent invader. When disease does develop, it is more frequently of the chronic type. Apparently some resistance or relative immunity does exist in those races exposed to the tubercle bacillus over long periods of time. How is this resistance to the disease brought about?

In 1890, Koch startled the world with the announcement that a cure for tuberculosis had been found. Tuberculin, obtained by filtration of glycerin-veal bouillon on which tubercle bacilli had been grown and eventually killed by boiling, was the new agent. Many therapeutic trials of this remedy proved its inability to cure the disease, but its experimental use provided much of value in the study of tuberculosis and of immunity to the disease.

In experimental work, Koch found that an animal once infected with tubercle bacilli reacted more quickly and violently to a second infection. This reaction was characterized by early inflammation going on to necrosis. The lesion finally showed a great tendency to healing by fibrosis. This phenomenon meant that an infected animal was more or less resistant to renewed or second infection. The early inflammatory reaction following a second infection was found to be closely simulated when tuberculin was injected in a previously infected animal. In 1907, von Pirquet demonstrated hypersensitiveness of the skin to tuberculin in previously infected children and called the changed reaction "allergy." Inasmuch as the amount of tuberculin absorbed in the von Pirquet test method is very indefinite, desire for more exact methods led to the use of the intradermic test of Moussou and Mantoux. By this method a definite amount of tuberculin is injected and absorbed. Many experimenters now thought

they had a means of estimating the existence and degree of resistance by the study of allergia. Upon this phenomenon are based many conclusions relative to the production of artificial immunity by vaccination.

The reaction of hypersensitiveness was at first thought to be entirely specific. Large amounts of tuberculin could be injected, even intravenously, into healthy animals and man without apparent harm (Ruppell, Engel and Bauer), whereas but very minute, almost infinitesimal doses were required to provoke violent local, focal and constitutional reactions in the infected or tuberculous. Later it was found that other substances, proteoses, etc., when given in sufficient (much larger) doses, could produce the same reactions in the tuberculous (Matthes, et al.). Many experiments showed that an animal sensitized specifically to a protein will usually react non-specifically to other proteins. It apparently is also non-specifically sensitized. The seat of the greatest reaction is located where the cells have had the longest exposure to the specific substances (focus of disease). For these reasons the reaction of hypersensitiveness is apparently not entirely specific. Yet the minute doses required to produce it when tuberculin is used in the tuberculous indicates that some specificity must exist. Histologically, there is no characteristic of the hypersensitive reaction to tuberculin (Blumenberg, et al.). It differs in no way from the reaction of irritation. Upon the concept of the meaning of the reaction of hypersensitiveness rests largely the idea of the value of vaccination. While hypersensitiveness is present as long as a focus exists, providing the disease is not overwhelming the host (e.g., in the preagonal state), and while it tends to diminish and possibly to disappear as the focus is healing or healed, in general no clinical parallelism can be established between the degree of reaction and the activity of the disease. Holman thought he could demonstrate this parallelism in individual patients and it apparently has been demonstrated in animals (A. Krause, Willis, Roemer, et al.). Nor has resistance or immunity been proved to exist (Roemer, Baldwin, A. Krause) without the existence of hypersensitiveness, unless the more recent questionable results of B-C-G (Bacille-Calmette-Guérin) can be substantiated.

AGENTS USED FOR VACCINATION

Vaccination in tuberculosis may be carried out by the use of intact tubercle bacilli or by bacillary products. Intact tubercle bacilli may be administered living or dead and the bacillary products as a whole or in part. The production of immunity or resistance in the non-infected differs from the object of vaccination in the tuberculous, in that the former is to prevent and the latter to cure disease. Reactions in the host in the two instances are entirely different. For this reason, prophylactic vaccination and its results will be considered first. It might be said here that, with the possible exception of pure tuberculoprotein, bacillary products will

not produce hypersensitiveness to tuberculin in non-infected animals (Zinsser and Petroff).

Living Bacilli

Vaccination with living tubercle bacilli may be attempted with (1) virulent, (2) attenuated and avirulent, and (3) heterologous strains of tubercle bacilli.

Living Virulent Bacilli.—That these bacilli conferred resistance to subsequent infection with virulent organisms was first shown by Koch. At the site of subsequent infection, inflammation rapidly occurred followed by ulceration which showed a great tendency to heal. His experiments were confirmed by Roemer. Roemer and Hamburger were able to demonstrate in guinea-pigs with chronic tuberculosis some resistance to moderate doses of virulent bacilli. Sheep which are naturally somewhat resistant could be rendered resistant to intravenous inoculations in doses sufficient to kill controls in four to six weeks (Roemer). Similar results were obtained in apes (R. Kraus), in guinea-pigs (Loewenstein, Lewandowsky, Courmont, Bruyant, Brown, Heise and Petroff, Baldwin, Roemer, A. Krause, and many others), in rabbits (Leber and others) and in cattle (Calmette, Pearson and Gilliland, and many others). Resistance may be brought about by any method of inoculation and is dependent upon the production and existence of tubercle formation which must not be severe enough to cause rapidly progressive disease (Roemer, Baldwin, A. Krause and many others). Selter found the highest resistance in those animals, guinea-pigs and calves, which had not only latent infection but in whose lymph glands virulent bacilli could be demonstrated. When all evidence of infection had subsided, R. Kraus, Gros and others found in apes no resistance to subsequent infection.

Probably the first to use virulent bacilli for vaccinating children were Webb and Williams. Previously they experimented with guinea-pigs and rabbits in which they found no tuberculosis at autopsy after giving at weekly intervals, extending over nine months, increasing doses reaching as high as 140,000 bacilli. Two children were inoculated in 1911, and another in 1914.

Two boys, one three months old, the other three years old, both children of a tuberculous father who died several weeks later and whose wife presumably had active tuberculosis, were inoculated. Living tubercle bacilli were given in the following doses: 1, 3, 5, 8, 12, 18, 25, 35, 50, 75, 100, 125, 150, a total of 607, from October 10, 1910, to January 12, 1911. Both children failed to react to the von Pirquet test previous to vaccination and in May, 1911, or four months later. They both remained well over this period. In 1914, they were again negative to a von Pirquet test (100 per cent tuberculin). January 20, 1913 (Webb and Gilbert), one child, living in a tuberculous milieu, was vaccinated with 2, 3,

5, 7, 10, 12 living bacilli. The von Pirquet test was negative before vaccination and for some time after. On March 9, a slight nodule appeared at a site of injection and later this grew larger and two others appeared. Bacilli were recovered from one of the larger nodules. March 19, 1913, a gland in the right axilla became enlarged and was removed. The child, however, remained healthy until June 14, 1914, the day of the last report.

Selter used an emulsion of ground tubercle bacilli composed of three living human strains of the 7th, 14th and 28th generations. He injected subcutaneously 10,000; 1000; 100; 60; 25, and 12 bacilli into nine children. Each child received one dose. In guinea-pigs, 100 to 1000 bacilli caused a slowly progressive disease and 100 bacilli or less no disease. The children were previously tested intracutaneously with 0.1 and 1 milligram old tuberculin and revealed no hypersensitiveness to tuberculin. They were approximately of the following ages: 3, 6, 10, 11, 12, 12, 23, 24 and 39 months. In each of the children receiving 10,000 and 1000 bacilli, a localized, cherry-sized abscess developed. In two, rupture of the abscess occurred and these were removed; in the remaining two, healing occurred spontaneously and without rupture. Only a very small nodule and no involvement of the regional lymphatics occurred in those receiving 100 bacilli and less. In some no local reaction could be seen. In those receiving 10,000 and 1000 bacilli, tuberculin hypersensitiveness developed in about four weeks and was marked. In those receiving 25 bacilli, tuberculin hypersensitiveness was noted in about forty days; and in those receiving 12 bacilli, only after three and one-half months. Those who received the larger doses retained the tuberculin hypersensitiveness at least fifteen months; and those receiving the smaller doses, only eleven months. In one child who received 50 bacilli, no tuberculin hypersensitiveness could be found even after three and one-half months. One of the children (60 bacilli) died of pneumonia (Grippe) about three months after vaccination with Selter's vaccine. At autopsy no generalized tuberculosis could be found. Selter gives no subsequent history of the other children.

From the experiments in animals, it is seen that a tuberculous focus is established by the use of virulent bacilli. In children the method is very dangerous. Control of the dose to produce only a retrogressive lesion is almost impossible, and control of the focus once established is even less possible. Intercurrent infections and other conditions in the child's life may cause the focus to become very active and lead to disastrous disease.

Living Attenuated Bacilli.—Calmette gives credit to Cavagnis as being probably the first to use attenuated bacilli. He used increasing doses of sputum to which had been added dilute carbolic acid. His animals, however, did not show satisfactory results. Grancher and Martin, in 1890, used bacilli attenuated by age, and later younger and more virulent bacilli. Their rabbits were more resistant to subsequent infection but not immune.

Richet and Hericourt had no greater success. Dixon, in 1889, and Trudeau, in 1893, using bacilli attenuated by age, demonstrated only partial immunity. The same conclusions were drawn by de Schweinitz, in 1894, and Pearson and Gilliland, in 1902. Arloing, by cultivating his bacilli on the bottom of a broth culture and shaking the culture frequently, obtained finally a culture of low virulence. With this he thought he obtained immunity, but other workers could not substantiate his findings. Theobald Smith used bovine bacilli, attenuated, but still sufficiently virulent to kill animals in doses of 10 milligrams. He discontinued it on account of its dangers.

Bacilli attenuated or killed by exposure to sunlight were used by Di Donna and Trudeau. Henry used ultraviolet rays. In no instance were results satisfactory.

Tubercle bacilli sensitized by the serum of a horse previously inoculated with dead and then with living virulent bacilli, were used by Vallée and Guinard. Tuberculin sensitiveness was not produced and the results were unsatisfactory. Fritz Meyer also used sensitized vaccine. Apparently it is less toxic than non-sensitized, but does not immunize.

Calmette and Guérin, by cultivating bovine bacilli on potato or agar, saturated with 5 per cent glycerinated bile, and carrying the organisms through subcultures on the same medium, were able to produce, after 230 subcultures, a very attenuated bacillus. After 70 subcultures the vaccine in a dose of 100 milligrams is well borne by calves, whereas the original strain, grown on ordinary media for the same number of subcultures, produces in a dose of 3 milligrams fatal tuberculosis in controls. This vaccine is called B-C-G (Bacille-Calmette-Guérin).

Calves were given (by mouth) two monthly doses of 5 to 20 milligrams of B-C-G. One month later, 3 milligrams of virulent bovine bacilli were given. No illness resulted and no tubercles could be found at autopsy as long as eighteen months later. However, when the tracheal or mediastinal glands of the treated animals were injected into guinea-pigs, a certain number developed tuberculosis, showing that the virulent organisms were harbored for some time. Rabbits, monkeys, guinea-pigs and other animals were used experimentally by the authors and by many others. Whether or not immunity is produced is yet an undecided question. Even the harmlessness of this vaccine has not been definitely determined, although Calmette claims it is avirulent in moderate doses for all varieties of domestic animals. That it does produce tuberculous changes which undergo resolution was shown by Schroetter, R. Kraus, Sternberg. Subsequent animal passage did not increase its virulence, in the work of Suarez, Schuurmann, Steckhoven, Tchechnovitzer and others. On the other hand, other workers occasionally produced tuberculosis by inoculation of B-C-G, viz., Nobel, Gerlach, R. Kraus, Selter, Petroff, the last even after a second passage through animals.

From animal experimentation it may be inferred that some resistance results from vaccination with B-C-G, no matter what mode of inoculation is used. However, the subcutaneous inoculation appears to give more resistance than the oral. Its use, however, is not free from danger, as tuberculosis is occasionally produced. Tuberculin hypersensitiveness follows only occasionally, and it is difficult, for this reason, to see how any great amount of resistance can follow oral administration.

Heterologous Strains.—Demonstrations of the non-pathogenicity of the human tubercle bacilli for animals led to attempts at vaccination by heterologous strains. Thus, Theobald Smith, von Behring, von Behring and Roemer and Ruppell, Hutyra, Lorenz, Thomassen, Pearson and Gilliland demonstrated in cattle the production of some resistance to subsequent virulent bovine infection. The partial immunity obtained persisted from several months to one year or longer. Theobald Smith and Griffith showed, however, that the human bacilli might be harbored for a long time in the animal body without evidence of disease, and that they might be eliminated through the udders of cows, although no disease of the udder existed. For this reason this method of vaccinating cattle has been discontinued. Neufeld, Neufeld and Miessner, Trudeau and Baldwin, among others, vaccinated asses and goats with human bacilli.

Bacilli from other sources, such as the slow-worm (Moeller), were employed, as well as avian bacilli (MacFadyean, Sheather, Edwards and Ninett), all producing a less evident resistance than that provoked by the human type.

Much interest has centered around the use of Friedman's turtle bacilli. Orth and Rabinowitsch demonstrated their long life in guinea-pigs with mild but typical tuberculous changes. Prolongation of life in the vaccinated as compared to control animals was observed by some workers. However, Kruse, in vaccinated guinea-pigs, found practically no reaction to tuberculin. The same was found by Bessau. Kruse reported on 319 children with negative von Pirquet reactions who were vaccinated with this strain. Two died of tuberculosis and in thirteen deaths the cause was not known. Obviously no information can be obtained as to its value. Szalai reported on 230 vaccinated infants under observation from two to five years. One child died of tuberculous meningitis. From the lack of statistical evidence and the failure to cause tuberculin hypersensitiveness, vaccination with Friedman's bacillus is only feebly, if at all, protective.

Moeller was probably the first to attempt immunization in man. He injected slow-worm bacilli into a vein of his arm and later injected "1/20 Oese" human bacilli intravenously. He did not become ill but lost a great deal of weight and took a long time to regain it.

Based upon his experiments in young calves, Calmette employed B-C-G in vaccinating children. For this purpose, he says, the culture should not be over twenty-five days old, nor the saline suspension older

than ten days. The suspension contains 500,000,000 (10 milligrams) bacilli to each cubic centimeter. Three doses of 1 c.c. each are given orally, at 48-hour intervals, in milk. (During infancy the gastro-intestinal tract is very permeable and presumably makes oral administration efficacious.) Infants only are vaccinated and this is performed on the third, fifth and seventh days after birth. In only about 6 per cent is tuberculin hypersensitiveness observed (Keller quoted by Bessau). In 1928, Calmette tabulated the results of vaccinating 52,772 infants over a period extending from July, 1924, to December, 1927. In 1924, 840; in 1925, 4,336; in 1926, 14,654; and in 1927, 39,942 were vaccinated. Of these infants, 6,219 were born in tuberculous families and 4,749 were observed from one to three and one-half years. Of 3,808 vaccinated less than one year previously, 118 or 3.1 per cent died. Calmette states that the mortality for the same ages of exposed and unexposed in France is 8.5 per cent. Thirty-four (0.9 per cent) died from tuberculosis, chiefly with meningitis. For the same ages living in a tuberculous milieu, Calmette says the rate fluctuates between 24 and 70+ per cent in the unvaccinated. Of 1,941 vaccinated one to three and one-half years previously, twenty-one (1.2 per cent) died and four (0.2 per cent) from tuberculosis. The general mortality rate in the unvaccinated is 1.6 per cent.

In his 1927 report, covering a period from July, 1924, to June, 1926, Calmette quotes mortality rates of 0.9 per cent for those vaccinated one to two years previously, and of 0.3 per cent for those vaccinated one-half to one year previously. He states that the mortality of infants living in a tuberculous milieu in France is 25 per cent in the non-vaccinated and only about 1 per cent in those vaccinated by his method. Petroff, in 1927, called attention to the confusion in Calmette's figures; in disputing Calmette's death rate he pointed out the fallacy of comparing the results in infants born in a tuberculous environment with those born in a non-tuberculous environment. Greenwood takes exception to Calmette's figures and states that the mortality rate of 25 per cent quoted by Calmette is far too high and does not agree with the statistical computations of Kjer-Peterson and Ostenfeld, and furthermore, and most important, that Calmette's use of statistics is ambiguous and erroneous. Rosenfeld deduces the infant mortality of France during the year 1925 to be 0.13 per cent, only one-seventh of the mortality (0.9 per cent) obtained by Calmette in his vaccinated infants. Bessau states that the general mortality rates in Germany and France are very similar and that the tuberculosis mortality rate is about 10 per cent of the general rate in France and Germany. In Germany, the tuberculosis mortality rate for the first year of life for those born alive in 1920 and 1921 was 0.15 per cent. In 1923, during the year of greatest price inflation, it was 0.19 per cent, and in Berlin, in 1923, it even reached 0.33 per cent, and in Leipzig, 0.48 per cent. In 1926, it had fallen to 0.15 per cent without any form of vaccination. Calmette, furthermore, after vaccination with

B-C-G, removes most of his children from the tuberculous milieu for three months or longer.

Vaccinations with B-C-G without any following deaths from tuberculosis are reported by Blanc, Cantacuzene, Rougebief and Bernard. Deaths from tuberculosis are reported by Moine (0.8 per cent), Birand (2.46 per cent), Ott (1.9 per cent) and Malvoz and Van Beneden (0.26 per cent).

Heimbeck narrates an interesting experience with B-C-G in pupil nurses at the Ullevaal Municipal Hospital in Oslo, Norway. Of 420 nurses entering training during the years 1924 to 1926 and part of 1927, 220 did not react to a von Pirquet test and 200 did react. All the nurses were apparently in good health. During the course of training, fifty pupils developed tuberculosis. Of these fifty, only two had reacted to a von Pirquet test on first entering the school. It would seem that the allergia possessed by the reactors gave immunity to superinfection.

Those pupils entering upon training in January, 1927, were given a von Pirquet test and the non-reactors were advised to try to establish allergia by the injection of B-C-G. Of the twenty-three non-reactors, twelve took B-C-G. A subcutaneous dose of 0.03 milligram was given at first and if no local reaction followed, 0.05 milligram was given. A reaction followed in from eleven days to eight weeks (an average of four weeks), which was characterized by a local inflammation of mild degree. Of the twenty-three who did not react to a previous von Pirquet test, those taking the B-C-G later developed allergia and, upon exposure to infection while nursing the tuberculous, none of these developed tuberculosis, whereas four of the non-allergic, who were not vaccinated with B-C-G, developed tuberculosis upon exposure to the tuberculous.

Much is lacking in detail regarding the health of the pupil nurses upon entering training. Radiograms apparently were not taken. The strength of tuberculin used is not mentioned, and the number developing tuberculosis after nursing the tuberculous (four of the twenty-three) for a period of only five months (January, 1927, to June, 1927, the date of the report), seems out of proportion to usual experience. No mention is made of the reasons for a diagnosis of tuberculosis.

Statistical proof of the prophylactic efficiency of B-C-G in children is most confusing and not at all satisfactory, and as yet by no means convincing.

Dead Bacilli

Dead tubercle bacilli have been used by many workers for vaccination without the establishment, in their judgment, of any appreciable immunity. A rapidly disappearing phase of increased resistance was established by Koch, Neufeld, Calmette, Deycke, Loewenstein, Schroeder, Noguchi, Babes and Proca, Trudeau and Baldwin, Kinghorn, Roemer, Baldwin,

A. Krause and many others. When heated enough to kill the bacilli, the bovovaccine of von Behring was no longer capable of producing immunity and Selter found his vital tuberculin inert after exposure to phenol, trypsin and pepsin, which destroyed the bacilli. Uhlenhuth and Joetten, using bacilli killed by trichlorethylene, by steam heat of 100° C., dry heat of 150° C. and also by antiformin, were not able to produce immunity to subsequent infection even when the infecting doses were small. Resistance, however, was increased, when bacilli killed by dry heat (150° C. for one-half hour) or by antiformin were used. This they thought was due to non-specific resistance and all the animals finally died of tuberculosis. Vaccination with bacilli killed by antiformin could not protect guinea-pigs, rabbits or cattle against the natural infection of a tuberculous environment. However, Prudden and Hodenpyl showed that the anatomic tubercle caused by injection of dead bacilli did not differ materially from that caused by living bacilli. Furthermore, tuberculin allergia in animals having previous injections of a sufficient number of dead tubercle bacilli could be demonstrated by Theobald Smith, Roemer, Trudeau, Baldwin, Bessau, Wolf-Eisner, Petroff, A. Krause and many others.

Langer thought he was able to produce immunity by vaccination with heat-killed bacilli (70° to 100° C.). His results could not be confirmed by Dold, Seligman and others. More recently, Petroff and Stewart, working together and making a very comprehensive study of the action of dead tubercle bacilli, found that the anatomic tubercle produced by dead bacilli was the same as that due to living bacilli. Tuberculin hypersensitiveness in the skin, pleura and testis was of the same character in each instance and lasted as long as 470 days in some animals. However, the dose of dead bacilli must be much larger than that of living, since the living propagate. The resistance produced by vaccination with dead bacilli was considerable, except to large doses of virulent bacilli.

These authors correctly criticize previous methods of testing resistance in the vaccinated animals, in that the number of virulent bacilli used has been far too large. Previous investigators measuring the dose by weight only would necessarily have many clumps of bacilli in their infecting dose, and the number of bacilli would be very uncertain. Doses of from 0.001 milligram (40,000 bacilli) to 5 milligrams (200,000,000 bacilli) were used to test resistance by previous workers, whereas as low as ten bacilli will cause tuberculosis in a guinea-pig. Obviously, enough bacilli to cause tuberculosis in thousands of animals were used to test the resistance of one vaccinated animal. With an infecting dose of 0.001 to 0.004 milligram and even 0.01 milligram, Petroff and Stewart found some prolongation of life in the vaccinated (forty-six days) and at autopsy much more macroscopic tuberculosis in the unvaccinated.

H. Langer, using dead (killed by heat) virulent bacilli, brought to rapid growth on media containing methylene-blue, and therefore young

cultures, vaccinated infants living in tuberculous environments. Fifty infants so vaccinated remained well during the periods of observation up to three years, which included physical and roentgenologic examinations. Bessau vaccinated 103 children, negative to tuberculin, with dead bacilli, of whom ninety-one (88 per cent) later gave a positive tuberculin reaction. Raw vaccinated 412 children from one and one-half to fourteen years of age with six injections of 0.001 to 0.006 milligram dead attenuated bovine bacilli at two weeks intervals. During four years of observation no child died of tuberculosis. Sanger vaccinated twenty-seven children intracutaneously. After three months he was able to discover tuberculin sensitiveness in twenty of these. Markedly positive reactions were seen in seven, moderately positive in five, weakly positive in three and no reaction in five. Fedders vaccinated sixty-two infants, previously non-sensitive to tuberculin given in any manner, with dead bacilli (Langer's method) and found that, later, fifty possessed tuberculin sensitiveness. Two or three months usually elapsed before sensitization manifested itself and for the test 1 milligram old tuberculin was given intracutaneously. No harmful effects were noted. The tuberculin sensitiveness could not be differentiated from that seen in the tuberculous. Intracutaneous revaccination in the allergic phase produced a reaction typical of a mild Koch phenomenon. Foreign protein in the vaccinated gave much stronger reactions than in the non-vaccinated, as happens also in the tuberculous. Faddick and Meyer vaccinated with Langer's vaccine twenty-six children living in a tuberculous environment but as yet not infected. Fourteen developed positive tuberculin tests on an average of 2.4 months later. Only nineteen could be observed for any length of time. Fourteen were exposed to tuberculosis for one year and five for two years. All had physical and roentgenographic examinations every six months. None showed subjective or objective evidence of tuberculosis. Furthermore, focal reactions were produced by subcutaneous inoculation of tuberculin. Klotz and E. Sanger, using Langer's vaccine, produced tuberculin sensitiveness in four or five children. When freshly made vaccine was used the results were much better. Ballin produced hypersensitiveness by vaccination with Langer's vaccine in seven or eight infants.

DISCUSSION

From experimental work in animals it is readily seen that hypersensitiveness to tuberculin is present after the animal has been infected with living tubercle bacilli; it persists as long as the focus exists and disappears as the focus becomes healed or the animal is overwhelmed with his disease. Immunity or even resistance to tuberculosis has not been proved in the absence of tuberculin hypersensitiveness. The reaction is non-specific histologically but specific in that only infinitesimal doses of tuberculin are

usually necessary to provoke it. It may well be chosen as one of the means of determining resistance, or of relative immunity, to tuberculosis.

Natural infection, such as occurs with half if not more of the human race to-day, produces by far the most marked and most lasting form of resistance or relative immunity to tuberculosis. Unfortunately, the dose and circumstances of infection are not under immediate control. Undoubtedly, living virulent tubercle bacilli in small numbers will produce relative immunity. But one is by no means sure when and where the focus of disease will end. The same dose may in one individual, under favorable circumstances, lead to marked protection, whereas in another, by reason of circumstances not under control, lead to disastrous disease. For this reason, vaccination with living virulent bacilli is wholly impracticable.

Numerous experiments in animals show that tuberculin hypersensitiveness can be produced by vaccination with attenuated and avirulent tubercle bacilli as well as heterologous strains. Almost invariably, the immunity or resistance produced is less marked and of shorter duration than when virulent bacilli are used. Furthermore, these living bacilli have been shown to live for considerable periods in the host and in cows; the human type bacilli may be given off for a year or more through the healthy udder. Transference from one animal to another occasionally causes generalized tuberculosis in the second animal. Recent work on dissociation of tubercle bacilli (Petroff, Branch and Steenken) and the determination of the characteristics of various types of tubercle bacilli leaves the idea of mutation of bacilli from one type to another still open to question. Whether immunity or resistance can be established without production of tuberculin hypersensitiveness, as Calmette with his oral method would lead us to believe, needs much further proof. For these reasons the use of attenuated or avirulent bacilli for vaccination is impracticable.

That dead tubercle bacilli in proper doses and prepared under proper conditions can and do produce tuberculin hypersensitiveness is certain. The allergia, as a rule, comes on slowly and is found in the majority of the vaccinated. The lesion of vaccination differs very little if any from that produced by living bacilli (anatomic tubercle). The hypersensitive reactions are in all respects the same as those caused by living bacilli. The resistance or relative immunity produced is, however, of shorter duration and of less value. Above all, the method is not at all dangerous. However, it would seem that infection occurring in a tuberculous milieu is not brought about very often by such overwhelming doses as were used experimentally in animals to test immunity. For this reason, in all probability, the degree of protection afforded by the production of hypersensitiveness to tuberculin and tubercle bacilli would be sufficient to localize (A. Krause, A. Krause and Willis, Opie) the small numbers of bacilli ordinarily entering the body and thereby prevent clinical disease. Whether or not it

is of practical value in protecting against disease, those infants exposed to infection will require years of statistical proof and close observation. Needless to say, it merits full investigation.

THERAPEUTIC VACCINATION

On the tuberculous host, tuberculin acts as an irritant, specific in the sense that only minute doses are required to produce inflammation at the focus of disease. Histologically the reaction is the same as that induced by other proteins, X-rays, sunlight, etc. Formerly it was thought that tuberculin was a true antigen, giving rise to tuberculosis antibodies, and that the tuberculin reaction was a true antigen-antibody reaction, fitting in with the theory of Ehrlich. We now know that tuberculin is not a true antigen and that the tuberculin reaction is not an anaphylactic reaction (A. Krause, Zinsser and Petroff). Tuberculin in its action as an irritant stimulates disintegration of the focus of disease, bringing about larger absorption of poisons from the bacilli and disintegrated tissue, and a consequent general reaction with fever and other symptoms of intoxication. When the irritant effect is not too strong, fibrous tissue formation is promoted, tending towards healing of the focus.

Tuberculin tolerance, in the majority of instances, can be brought about by gradually increasing doses, watching for mild reactions and waiting before giving the next dose for their subsidence. Tuberculin sensitiveness, some believe, can be increased by repeated injections of the same dose (Pickert and Loewenstein). Which of the two methods is better in tuberculin therapy is yet an undecided question. Schroeder, after thirty years' experience, believes that abolishing hypersensitiveness is a dangerous thing. During the stage of anergy, when the allergic reactions are absent, metastases have a tendency to occur and no noticeable healing takes place in the foci of the larynx, bones, joints, etc. For these reasons Schroeder thinks tuberculin therapy should be directed toward the maintenance and increase of allergia. In his investigations, use was made of blood sedimentation test, Arneth's count, complement fixation test, lymphocyte count, etc.

For treatment, the majority of workers select those patients whose lesions show a tendency to fibrosis. Those with exudative pulmonary lesions may be treated only with the greatest caution. On the other hand, when no fever is present, symptoms are abating and the focus shows evidence of healing in the presence of definite allergia, tuberculin treatment is not needed. When resistance fades, allergia wanes and fever has a tendency to occur or is of a low grade, tuberculin may, when there is a tendency to fibrosis at the focus, stimulate allergia and promote further healing. Tuberculin should not be given when marked exudative processes occur nor when the patient has marked disturbances of the circulatory and nervous systems and when high fever is present for a long time.

Statistically, there is no proof that tuberculin acts as an immunizing agent. Literature citing marked benefits from its use is no more prevalent, perhaps, than that showing its ineffectiveness. In individual cases, for no apparent reason, almost all who have used it have occasionally (in 1 to 2 per cent) seen brilliant results. Experimentally, in foci of the eyes, skin and other visible portions of the body, good results have been observed and the same may be said to be true of such lesions in man. In the treatment of pulmonary tuberculosis at Trudeau, there was living after a number of years a slightly larger number of tuberculin-treated patients than of the non-tuberculin treated. The difference, however, was small and might be explained in part by the margin of error. Other statistics show a larger number losing tubercle bacilli from their sputum and more with a greater capacity for work in after years. These reports are, however, not wholly conclusive and fail to convince many doubters.

The number of preparations used therapeutically is very large and is being added to as time goes on. This in itself is an admission of the ineffectiveness of all previous preparations. Broth filtrates of bacilli, heated and unheated, watery extracts, compression juices, extracts with various chemicals, viz., halogens, phosphoric acid, alcohol, ether, olive oil, nucleic acid, sulphuric acid, lecithin, neurin, etc., of virulent and avirulent, acid fast and non-acid fast, human and bovine, avian and piscine, have all been used; and in addition to many others, emulsions of crushed and intact dead bacilli of various strains and types. At the Trudeau Sanatorium, dead "R" and "S" bacilli (dissociated colonies) were used subcutaneously in a few patients with progressive chronic disease, but no conclusive evidence of any benefit was obtained. Method of administration and dose vary considerably; some may have peculiarities of reaction that differ from others, biologically and serologically, but fundamentally the results are the same. For action they all depend on the maintenance or increase of allergia, detoxication of the patient and fibrosis at the focus of infection. One weakness of tuberculin therapy is the lack of a method for the proper standardization of the agent which would permit comparison of the work of different investigators. This weakness may soon be overcome by the work at the United States Department of Agriculture on standardization, and of Florence Seibert on the isolation of a crystalline preparation.

Intravenous, subcutaneous, intracutaneous, percutaneous and cutaneous methods, while differing necessarily in dose, apparently do not differ in results, as was thought by Sahli, Pondorff, Moro, Klaus Schilling, Petruschky and others. Oral administration is apparently little if at all effective with most tuberculins.

Administration.—For therapeutic use old tuberculin (O.T.) must be much diluted. The original solution is first diluted in the proportion of one part of tuberculin to nine parts of physiologic saline to which has been

added 0.25 per cent phenol. Each cubic centimeter of the dilution will then contain 0.1 c.c. O.T. Further dilutions down the scale are made in the same way. One c.c. of dilution No. 1 is added to 9 c.c. of the phenol-saline diluent to make dilution No. 2, of which each c.c. contains 0.01 c.c. O.T., etc. For convenience in charting, the dilutions may be labeled in the form of a fraction, the numerator of which expresses the number of zeros after the decimal point and the denominator the numerical designation of tuberculin. Thus, dilution 0.01 would be expressed 1/1 and each c.c. would contain 0.01 O.T. Dilution 4/1 would signify 0.00001, of which 1 c.c. would contain 0.00001 c.c. O.T., etc. With a syringe graduated in 0.01 c.c., very minute doses can be safely measured. Subcutaneous administration may be begun with doses less than that necessary to produce a general reaction. To determine the first dose, the intracutaneous test is given beforehand. Beginning with 0.1 c.c. of 5/1 dilution (6/1 or 0.0000001 O.T.), the dose is increased tenfold, *e.g.*, 5/1, 4/1, 3/1, 2/1, etc., every three or four days until an inflammatory reaction measuring 18 to 20 millimeters is produced. Experience shows this method estimates, as nearly accurate as is possible, the general reacting dose. Usually, a dose ten times the skin reacting dose (20 millimeters) will produce a general reaction. Care must be exercised to place the tuberculin *into* and not under the skin.

One-tenth of the skin reacting dose may be safely given subcutaneously and the doses gradually increased, logarithmically (the same per cent increase for each dose) or otherwise, as long as symptoms of a general or focal (lung) reaction are not produced. Doses may be given every third or fourth day or at longer intervals. The patient should rest after each dose until the lapse of eight or ten hours, during which period a reaction usually occurs if at all. Injections are best given, therefore, in the morning or at night, so that the patient will be awake when a reaction might occur. Reactions are of course dangerous and should be avoided except by the very experienced. Tuberculin tolerance can be gradually increased by the foregoing method.

Some begin treatment with very minute doses in all individuals (6/1 0.0000001 c.c. O.T., or even less) and proceed with very slowly increasing doses. Others (Loewenstein, *et al.*), by injecting the same dose repeatedly, expect to increase tuberculin hypersensitiveness.

Tuberculin should not be given therapeutically by any but the experienced. Care must be exercised in preventing serious focal and general reactions. The patient should keep a daily record of his symptoms and of his temperature and pulse at frequent intervals during the day (every four hours at least), so that the milder reactions can be detected and the severe ones avoided. When the tuberculous lesion is visible it must be critically examined after each dose to detect focal reactions which must never be severe.

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COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS

WILLARD B. SOPER

GENERAL CONSIDERATIONS

Numerous measures have been proposed for the cure of pulmonary tuberculosis, but rest still remains the most valuable treatment. Functional rest of the lungs through actual rest in bed or bodily rest is admitted to be the greatest factor in the present treatment employed in sanatoria.

Collapse therapy, proposed more than a century ago, has but recently come into its own. It has added to the treatment of pulmonary tuberculosis a new interest, and from all parts of the world has been steadily accumulating an enormous literature of study, improved knowledge and good results. Other proposed remedies are applicable to the minimal case where diagnosis is often open to question and cures may reasonably be expected. Collapse therapy, on the other hand, finds its field in severe disease, very often in the otherwise hopeless case. The effect at times is astounding in its restoration of doomed individuals to satisfactory health. The phthisiotherapist has derived new hope and enthusiasm as each year sees wider and more successful application of the methods.

In 1821, James Carson, of Liverpool, saw the possibilities of artificial pneumothorax. But he was a physiologist and the idea did not reach beyond the laboratory.

In 1880, there came from Potains Clinic, in Paris, reports of three successful cases treated by artificial pneumothorax, but the possibilities were still not realized. Forlanini, in Italy, saw the light. His first case was treated in 1888. In 1894, he published his first two cases, then some others, then remained silent until 1906. Meanwhile, James B. Murphy of Chicago, in 1898, proposed pneumothorax as a rational method and treated five cases. His pupil, Lemke, in 1901, reported the treatment of fifty-three cases. Brauer, in Germany, became interested and began reporting his work in 1905. Then Forlanini broke his silence in 1906 with twenty-five cases. Saugmann of Denmark, in 1904, introduced the manometer.

Artificial pneumothorax was now fairly launched. From Germany, Denmark, France, Switzerland came reports. The names of Brauer, Saugmann, Küss, Dumarest, Spengler, and von Muralt are associated with the earlier days. In the United States, Mary Lapham published her first

paper in 1911, and Robinson and Floyd followed, in 1912. Since then the names have become legion.

The other forms of collapse therapy have been developed in an effort to bring about the same beneficial results achieved by artificial pneumothorax, but in such cases as were unsuitable for the latter treatment, owing to too extensive adhesions between lung and chest walls. For a more detailed history of the development of these operations, the writer is referred to the excellent monograph of John Alexander on *Surgery of Pulmonary Tuberculosis.*

Rib resection to relax the tuberculous lung was first performed by de Cérenville of Lausanne, in 1885. Operations were modified by different surgeons, but results were never satisfactory until Gourdet of Nantes, in 1895, showed experimentally that by cutting the ribs paravertebrally as near as possible to the transverse processes much less actual rib had to be excised to effect almost complete collapse of the bony chest wall. Brauer, Friedrich, Wilms and Sauerbruch have developed the fundamental technic of present day thoracoplasty.

Other operative procedures to supplement the effect of pneumothorax and thoracoplasty or to meet special conditions have been devised, *e.g.,* phrenicotomy, extrapleural pneumolysis, intrapleural pneumolysis.

MECHANISM AND EFFECT OF COLLAPSE THERAPY

Under the term collapse therapy are included the several surgical measures employed to produce a localized or entire collapse of a lung with a view to giving the affected part a more complete rest than otherwise possible. Collapse therapy as a term comprehends contraction, compression, demobilization and subsequent reëxpansion. While earlier surgical measures have been discarded those comprised under this term are establishing themselves daily more and more as a great advance in the treatment of certain selected cases of lung disease, particularly tuberculosis.

The modern conception of tuberculosis as a generalized infection, and the anatomy and physiology of the chest organs render inadvisable an excision of tuberculous areas or foci in the lungs. On the other hand, collapse therapy is in harmony with nature's method of cure and serves to complete in part or in whole the natural attempt at demobilization.

The manner in which collapse therapy exerts its favorable influence is still known only in part. Demobilization of the diseased area may be said to restrict the production and circulation of toxic substances and in corresponding degree to increase the resisting power of the patient. The flow of lymph is impeded or the lymph-vessels are actually blocked. There is apparently an increased flow of blood to the affected part, thus aiding repair through congestion. The presence of air in the pleural space in

artificial pneumothorax permits the diseased lung to withdraw from the chest wall. It can thus more completely undergo the retraction which it attempts and can accomplish only in small part without the pneumothorax. Scar tissue forms more quickly and more permanently; cavities of a size which close only very rarely under the usual circumstances may disappear relatively quickly when collapsed.

One of the most beneficial effects is that upon the production and raising of sputum. This may be caused to dry up in whole or in part and the degree of this particular effect is of vital importance to the patient's welfare. The newer observations of iodized oil being carried by the act of coughing to parts of the lung remote from that into which it was introduced indicate the frequency with which bacillus-containing sputum is transported into healthy lung tissue. The wonder is, as Archibald implies, that bronchogenic spread of disease by coughing is not even more extensive than is actually the case. In so far as sputum can be eliminated the spread of disease is checked, not only in the lungs but in the larnyx, intestines and other organs.

With the newer operative procedures carried out without the opening of the pleural sac, the organs within the thorax are permitted to adapt themselves relatively gradually and with success to the changed conditions. Even with an entire lung rendered functionless by collapse, the relatively sound lung is found quite capable of assuming the added burden. This it does increasingly well through a compensatory hypertrophy, analogous to that of other organs where one of a pair ceases to function. This adaptation is seen not only in the respiratory apparatus but also in the circulatory, which, when the therapy is properly applied, appears to suffer little or not at all.

Choice of Methods in Collapse Therapy.—As already stated, all forms of collapse therapy aim at the same result. There is an order of simplicity and effectiveness which, other things being equal, determines the choice.

Artificial pneumothorax is employed most frequently, as the simplest and usually most satisfactory method. It is applied gradually, thereby allowing the lungs and circulation to adapt themselves to it; it can be controlled in the sense that gas can be withdrawn if desirable; by discontinuing its use, the lung, when healed, may reëxpand; there is no difficult or scarring operation; as a method it is simple and is daily performed by large numbers of physicians unqualified to perform the other forms of operation; it presents the minimum of serious complications.

ARTIFICIAL PNEUMOTHORAX

Indications.—The disease should be essentially unilateral and the lesions compressible. It should be possible for the patient economically and otherwise to carry out the treatment.

With the above requirements sufficiently satisfied, what should determine the decision to interfere? Generally it is the patient's failure to respond to the usual conservative measures; in other words, the prognosis is doubtful or bad. Not seldom the prognosis is obviously hopeless from the outset with any treatment except the surgical. Once the future offers nothing by ordinary methods, interference is indicated; and the earlier the better because adhesions are the bugbear of pneumothorax and they increase with time, although this statement does not always hold good. Then, too, delay means prolongation of treatment and may mean spread of disease.

Types of Lesions.—A classical case is that of clinically unilateral tuberculosis. While there are but few patients that come strictly into this group, there is a relatively large number in whom the disease in the better lung is so slight or so inactive that for practical purposes the disease may be regarded as unilateral. Such cases, then, must make up the majority of those suitable for collapse.

In the early days of the treatment much was written as to the relative promise and dangers of different types of lesions. Nowadays one hears much less of this. Apical tuberculosis with its tendency to retraction and healing still offers perhaps the best prognosis as also fibrocaseous disease in its different manifestations. Pneumonic conditions were formerly regarded as unfavorable. The swing is now away from this point of view. Obviously they should not contract too suddenly, but if they are allowed to collapse slowly the results with these acute rapidly progressive lesions are often most striking. One great advantage of treating them early is the fact that they tend to become adherent or to excavate at an early date, and if one is to anticipate these events he must perform collapse at the earliest moment. So while one may theorize more or less on the relative merits of different types of lesions the collapse treatment is not withheld for any period of time where the other requirements are fulfilled and the patient is not responding well to ordinary conservative treatment.

Hemoptysis.—Hemoptysis of any extent is always a menace because it so often spreads disease. Pneumothorax here finds often a prime indication. The literature contains much as to the mechanics of the beneficial action of collapse and the quantity of gas to be insufflated. It used to be believed that large quantities should be given with a view to an actual compression of the bleeding area. This method would appear to be condemned on several counts: The operator is not always certain as to the bleeding side; he is never certain that the bleeding area is not bound to the chest wall by adhesions; there is the possibility of inducing an aspiration pneumonia. Smaller amounts of air or gas are now more in vogue for several reasons; the lessening of tension alone may be enough to stop bleeding; there is much less danger of a physiological upset of circulation and respiration; the danger of aspiration pneumonia is greatly reduced;

discomfort to the patient is minimized; in case the bleeding portion of the lung is bound by adhesions, the remainder of the lung will not be collapsed suddenly and an added burden thrown upon the bleeding area. A conservative method recommends itself of introducing some 200 c.c. of air or gas, awaiting results for one or two hours and repeating the procedure as indications arise.

Cavitation.—Cavities of any size are generally a menace to life, although this rule does not always hold. When sputum is positive it is fair to assume there is activity in the walls or surrounding tissue. Pneumothorax would be the method of choice for the collapse of the antra, but unfortunately too often the cavity is so bound to the chest wall that this treatment is ineffectual. In such event other forms of collapse therapy should be considered.

Spontaneous Pneumothorax.—When this condition occurs and the opposite lung is sufficiently sound, it is often good practice to continue the pneumothorax in the event that the rent in the lung has closed. Should fluid develop it may be replaced by air, or the proper pressure maintained in the pleural cavity until the fluid is absorbed or there is occasion for other treatment.

Persistence of Positive Sputum.—When tubercle bacilli persist in the sputum despite reasonably prolonged conservative measures, pneumothorax may be indicated to obviate the danger of their presence. Guinard, in France, has recently stressed this indication particularly by once more advancing figures to show the ultimately great danger of the persistence of bacillus-containing sputum.

Pleural Effusion.—Inflammation of the pleura with exudate is, according to the present conception of its being, an allergic response to new bacilli implanted upon an allergic pleura, always associated with disease of the lungs. The latter, however, may be slight. If it is of any extent and the opposite lung is in good condition, as is usually the case, the fluid may be replaced by air and the patient's ultimate restoration to health be much more probable. To allow for a reaccumulation of fluid, about one-third as much air or gas should be introduced as there has been fluid withdrawn. The replacement of fluid by gas has other advantages: It permits the removal of larger quantities of fluid without the physiological effect of too great lowering of pressure in the pleural cavity; it prevents the formation of adhesions between lung and chest wall which so frequently follows pleurisy with effusion, and thereby prevents any subsequently desirable collapse of the lung by pneumothorax. The conversion of a tuberculous empyema into a pyopneumothorax is excellent practice and greatly facilitates treatment of the empyema by aspiration and the washing method.

Tuberculosis of the Larynx.—This complication was at first considered a contra-indication, but has come to be regarded as the opposite.

Some still maintain the old point of view, but St. Clair Thomson sees the only contra-indication in miliary inflammation. When cough can be allayed and the sputum rendered free from bacilli by artificial pneumothorax, the larynx is afforded a great advantage and is actually found as a rule to respond surprisingly favorably. It would appear that the advantages derived in early involvement would apply equally in later involvement. Given, then, a case doubtful with regard to the lungs, the presence of positive sputum and laryngeal involvement would turn the scale to the pneumothorax.

Pregnancy and Tuberculosis.—The dreaded occurrence of pregnancy during tuberculosis, or the still more dreaded development of tuberculosis during pregnancy, often may be satisfactorily combated where a sufficient collapse of the single diseased lung may be obtained. Rist, of Paris, is particularly insistent upon this indication. If the lung disease is essentially unilateral and the continuation of pregnancy is desirable or necessary or when the condition of pregnancy has progressed beyond the period of non-dangerous therapeutic abortion, pneumothorax should come in for consideration. Where pregnancy occurs during already instituted pneumothorax treatment, abortion may very often be dispensed with.

Economic and Social Indications.—When a wage earner must be restored in a minimum of time; where a patient will be obliged to return to his family with sputum still positive; where a patient has obviously too little moral stamina to successfully carry out his cure—under all these circumstances, a successful pneumothorax or some other form of collapse therapy may solve the problem.

A further and often great advantage in pneumothorax lies in the necessity of refills which, on first thought, may appear a disadvantage. The patient is obliged to keep himself under observation and is restrained from jeopardizing his hard-earned results through ignorance or carelessness.

Diabetes.—There is still some dispute as to the advisability of lung collapse in the presence of complicating diabetes. However, considering the seriousness of the prognosis, pneumothorax should be employed where the lung condition fulfills the requirements. Pneumothorax should control the spread of the disease while insulin controls the diabetes.

CONTRA-INDICATIONS

Age.—Older persons are believed to react less favorably than the young. If, however, one discounts the greater probability of adhesions which thwart the treatment, the arguments are not convincing. Generally speaking, if the indication is present and the prognosis calls for it, the treatment need not be withheld.

Emphysema and Asthma.—Advanced emphysema and asthma are regarded as contra-indications. In the case of asthma, however, with only

one lung tuberculous, the pneumothorax would have to be seriously considered.

Circulatory Disorders.—The fact that the heart and vessels are not entirely sound is not in itself a contra-indication. Obviously, however, with a circulation much impaired, one would hesitate to put an extra strain on the right heart by collapsing the lung to any great extent.

Kidney Disease.—Disease of the kidneys should not constitute a contra-indication unless severe. It may even be caused by the lung condition, in which event improvement in the latter would work to the advantage of the kidneys.

Intestinal Tuberculosis.—Although regarded as a contra-indication in the early days, it is difficult to accept that a treatment which, if successful, lessens toxemia, dries up the sputum, and improves the patient generally, can have any but a beneficial effect upon the intestinal tract. The writer knows of no study of the occurrence of intestinal tuberculosis under already existing fairly successful collapse therapy. It is his opinion that intestinal, like all other complications, are prevented in proportion to the good effect of the collapse upon the lung condition. Reasoning from the very high incidence of intestinal tuberculosis in association with cavity formation in the lungs, any treatment which obliterates lung cavities conduces to the prevention and cure of the dreaded intestinal complication.

COMPLICATIONS

The commonest complication by far is the occurrence of fluid. In the experience of careful observers, this manifests itself sooner or later in approximately 50 per cent of cases. The amount is often small and the symptoms likely to be overlooked if the case is not frequently checked by X-ray. Again it may occur much like an ordinary pleurisy with effusion, its onset sudden or gradual and causing fever and constitutional symptoms ranging from slight to severe degree. Usually the effusion quantity does not become excessive, but again it may reach a degree requiring the removal of sufficient fluid or gas to lower the increased pressure. This fulminating type, requiring at times several aspirations of fluid, develops in approximately 5 per cent of cases into tuberculous empyema and then presents a new problem of treatment. For the treatment of tuberculous empyema the reader is referred to the textbooks on pulmonary surgery.

Another complication which fortunately occurs rarely is rupture of the lung. The lung rupture may heal quickly without severe results, or a so-called valve action may exist with more air entering through the rupture than escaping from it; or, finally, a bronchopleural fistula may be produced with the inevitable production of a mixed infection empyema.

Fluid usually develops and often becomes purulent. It may be necessary to withdraw gas on one or two occasions in order to relieve the excess pressure in the pleura. Too much gas should not be withdrawn, because the greater the pressure the better is the chance for the closure of the opening in the lung.

The rarer complications depending immediately upon technic, comprising air embolism, pleural shock and cutaneous emphysema, will be discussed under "technic."

ADHESIONS

In theory, artificial pneumothorax should be ideal, but a number of factors militate against it. The chief of these is the presence of pleural adhesions, preventing adequate collapse of the diseased area. Their presence can be no more than surmised without the actual attempt at treatment, and, often, one's surmise is wrong, not only as to the presence but also as to the absence of adhesions. Speaking generally, the older the process and the more pleurisy in the past, particularly with effusion, the greater is the probability of adhesions. Adhesions may be located anywhere, but are apt to overlie the severe lesions. They may separate or stretch and thus permit a sufficiently partial or complete collapse, or again prevent completely the collapse of the part especially requiring it. In about 20 per cent of cases otherwise suitable for pneumothorax, the pleural space cannot be located on account of adhesions.

If adhesions prevent an effective collapse of the part involved, other procedures may still bring about the desired result; namely, phrenicotomy, pneumolysis, and thoracoplasty, all of which will be described later.

TECHNIC

The standard textbooks in English, particularly that of Riviere, go into such detail that the reader is referred to them. Numerous forms of apparatus are on the market. All have certain essential features. Some sort of manometer, generally a U-tube water manometer, is indispensable. It registers the pressure within the pleural cavity before, during and after insufflation.

The air or gas to be insufflated is usually contained in a glass cylinder, etched in cubic centimeters to indicate the amount of gas injected. A movable second glass cylinder, containing water or an antiseptic liquid and open to the air, is connected by rubber tubing with the first. When the second bottle is raised, the fluid flows to the other, thereby displacing the gas out of the first through a rubber tube, connected with the needle which is introduced through the chest wall.

The illustration (Fig. 1) is of the Robinson apparatus, a form rather widely used in this country. A number of different forms of needles are

in use. The one illustrated (Fig. 2) differs only slightly from the many forms used abroad. The larger blunt needle is generally employed at the first insufflation and often at the second to avoid as far as possible any
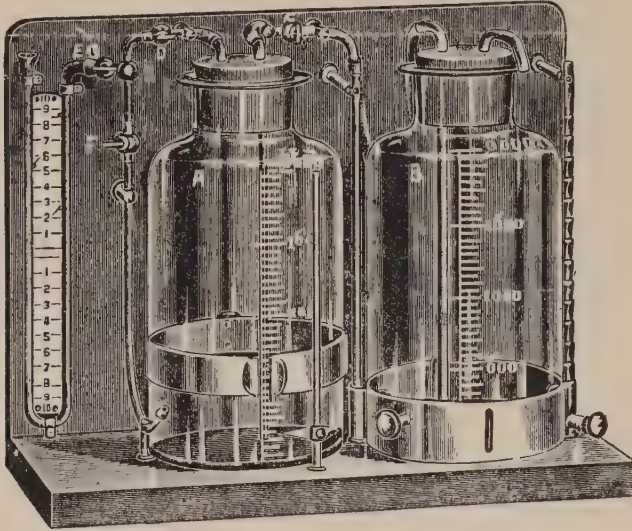
FIG. 1.—ROBINSON'S APPARATUS FOR ARTIFICIAL PNEUMOTHORAX.
(Made by Codman and Shurtleff, Inc., Boston, Mass.)

injury to the lung. Smaller needles are employed when the gas space has been established.

The gas used in the beginning was nitrogen, on the theory that its absorption was slower. Investigations have demonstrated that the absorp-
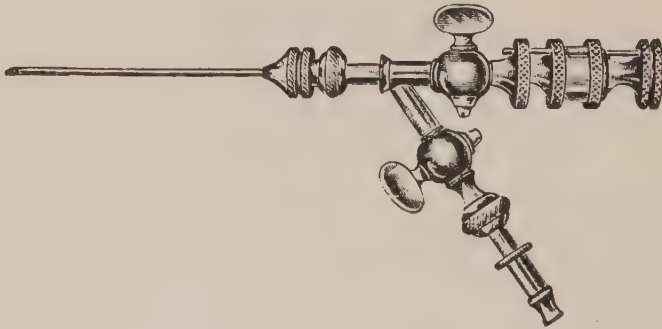
FIG. 2.—FLOYD NEEDLE.
(Made by Codman and Shurtleff, Inc., Boston, Mass.)

tion time of nitrogen and air is practically identical. Therefore, the use of air on account of its cheapness and availability has become wide-spread.

Initiation of Artificial Pneumothorax

The needle is usually introduced in the lower part of the thorax where the probability of adhesions is less, preferably in a spot where percussion note and other physical signs suggest their absence. There are two sites of selection—one in the anterior or midaxillary line, and the other in the back below the angle of the scapula. One is more apt to succeed in the axilla because here the excursion of the lung is the greatest. Not seldom the patient prefers not to see the operation and the back is selected. The patient is placed either on his back or half prone, with pillows underneath the body to properly raise the selected part and to separate the ribs. The arm on the affected side is elevated above the head to bring still greater separation. A local anesthetic is used, not only to relieve the patient of any pain, but also on the theory that it helps to prevent pleural shock. A little patience on the part of the operator is all that is necessary in order to make the procedure practically painless. Novocain, 1 per cent solution, is best. Perform the initial filling with the minimum of circumstance, treat the matter lightly as a minor affair and not as an operation with all the preliminaries of an operation. It can, for example, be performed in the patient's own bed instead of in an operating pavilion. Codein, ¼ grain, under the tongue, or the same amount in syrup, given, when preparations are begun, will serve to allay cough and quiet the patient. It is needless to state that the skin should be sterilized with iodin or mercurochrome and that needles should be very carefully sterilized.

The complications of the initial insufflation have been reduced greatly with improved apparatus and technic, especially with the introduction of the water manometer by Saugmann.

Pleural shock presents symptoms usually indistinguishable from those of gas embolism. The typical case becomes pallid, loses consciousness, and becomes cyanosed. The pupils enlarge, respiration and pulse become irregular, and muscle spasm may ensue. Cases may show only the slightest symptoms or the most severe, even to death. The symptoms may reappear with refills and when such is the case more than once, the pneumothorax treatment may have to be discontinued. The needle should be withdrawn immediately and measures for stimulation of heart and respiration instituted at once. Fortunately the severe and fatal forms of shock are quite rare. Many workers have never seen them. Stivelmann found none among 867 cases treated by nineteen American workers. Others have met one or two among several hundred insufflations.

Gas embolism, fortunately, is also rare, but is a definite danger. Gas or air may gain entrance to a branch of a pulmonary vein through injury of the lung or thickened pleura, and be carried to the left heart and thence to the brain or, with the needle accidentally in a vein, the gas may be sucked from the tubing when it is opened to the needle.

A third complication, most commonly occurring in the beginning, is *cutaneous emphysema*. Coughing during or immediately after insufflation may raise the intrapleural pressure sufficiently to force gas out through the hole made by the needle in the parietal pleura and thence into the tissues. The symptoms are those ordinarily encountered in cutaneous emphysema. The distribution may be quite extensive and rather painful but the condition is not dangerous and subsides in a few days. It may usually be prevented by using a needle not too large, by preventing cough during and immediately after puncture, by applying a tight bandage for an hour or two after puncture, and by so manipulating the tissues as to obliterate the needle track on withdrawal.

A deep form of emphysema also occurs as a rare complication. Gas may enter the interstitial lung tissue through a wound of the lung or may travel between the parietal pleura and endothoracic fascia. In either case it appears in the mediastinum to cause tightness and difficulty in swallowing, or even cyanosis. However, no harm results and the condition cares for itself.

Lung puncture must frequently take place without harmful effect. On the other hand, it may produce a rapid collapse of the lung, or, in very rare cases, produce a dangerous perforation of the lung, leading to pyopneumothorax.

The possibility of these rare complications makes a proper technic indispensable, but should never deter one from employing pneumothorax.

Maintenance of the Pneumothorax

No rules can be laid down here. The more closely the patient is followed clinically and by X-ray, the better the results. Insufflations subsequent to the first are given at intervals of two to five days, according to circumstances, the object being to replace the constantly absorbing air and each time advance the collapse a little farther. Some cases may be pushed faster than others, depending upon adhesions and the character of the lesions. A pneumonic case, for example, would be collapsed more slowly. According to Küss, there comes a time after a few insufflations when an optimum collapse is attained. This is judged by clinical symptoms, X-ray examinations, physical signs and manometer pressures. It is that degree of pressure which is considered the most satisfactory for the moment. In most instances it is reached when the mean of the manometer readings is zero or a little below zero, which is the atmospheric pressure existing in the lung. Leuret, of Bordeaux, stresses the point that up to this time the lung has merely been collapsing of its own elasticity. Not until the pressure is above zero does actual compression take place. Most operators prefer to hold the mean pressure at zero or a little below. There is less risk of tearing the lung. Adhesions, when they exist, will often stretch

under the lower pressures and the ultimate result will be equally satis-
factory with less risk. There are patients in whom, following fluid forma-
tion, the lung is obviously threatening to adhere to the chest wall, and the
success of the pneumothorax is threatened. In these cases higher pressures
may be warranted. In general, however, one should be well experienced and
there should be a definite indication before the pressure is raised above zero.

Often the manometer reading will show a surprising drop from a
previous reading, particularly early in the treatment. This may be due to
an enlargement of the pleural space by the separation of adhesions. Again
the pleura may take a surprising amount of gas without commensurate
effect upon the pressure. This event is usually due to a shifting of a
movable mediastinum. Again the pressure may be surprisingly high before
beginning a refill. Here one suspects fluid to be occupying a portion of
the space.

The later refills are spaced in point of time in such a way that the
optimum pressure can be reëstablished with a proper amount of gas. Many
feel that 600 c.c. of gas are a maximum for a given refill. A few give
more. Some prefer less where the facilities are at hand and make more
frequent refills a simple matter. More frequent refills appear more logical
since the lung reëxpands less and is less violently recollapsed. Many are
the arguments as to pressure and quantity of gas and intervals of refill.
The wise course seems to be—and more come to it every day—to use the
lowest pressure possible to attain the desired results. Proceed gently and
slowly. Thus complications are kept at a minimum.

RESULTS OF COLLAPSE THERAPY

The ultimate results of the various forms of collapse therapy are
essentially the same. When satisfactory, the treatment is followed by an
improvement in all general respects. The patient loses his toxic symptoms,
becomes brighter, and ceases to lose weight. Appetite is regained, and tem-
perature, pulse and respiration gradually fall. It should be added here that
there may be a temporary increase of symptoms, especially in thoraco-
plasty, owing to a sudden increase of absorption; but this is of relatively
short duration and is not surprising in cases where any degree of tubercu-
lous pneumonia is present.

Perhaps the most significant, satisfactory result is the decrease of
sputum, even to the point of complete disappearance. The bacilli become
steadily fewer until absent. This result in itself is of great importance,
for herewith the danger of bronchogenic spread as well as the chance of
spread to other organs is greatly reduced or ended. Unfortunately this
desired result may be only partially achieved by the first procedure of
employing artificial pneumothorax, and another form of collapse therapy
may be required to supplement the first.

As to results from economic and sociological standpoints, the worker is restored much earlier to partial or full working capacity; the patient returns to his old environment, no longer disseminating bacilli.

Statistical Results of Artificial Pneumothorax

Up to October, 1924, Gravesen, from the Vejlefjord Sanatorium, Denmark, reported 675 cases in which artificial pneumothorax was performed or attempted. Two died at the introductory injection, an operative mortality of less than 0.3 per cent for all cases. Of the 675 patients, 275 had been discharged from sanatoria prior to January 1, 1917. Of the 257 discharged, artificial pneumothorax had proven practicable in 172. In eighty-five cases pneumothorax of any size could not be induced. The state of health of these two groups in January, 1919 (*i.e.,* two to twelve years after discharge from sanatorium), was as follows:

State of Health	Artificial Pneumothorax Practicable ..		Artificial Pneumothorax Impracticable	
	Number	Per Cent	Number	Per Cent
Able to work	55	32.0	9	10.6
Not able to work	5	2.9	3	3.5
Died from tuberculosis	109	63.4	71	83.5
Died from other causes	3	1.7	..	...
Unknown	..	...	2	2.4

Gravesen, like many others, finds the chief reason for failure to lie in adhesions. He presents groups very interesting in regard to this fact.

Group 1.—Cases of complete pneumothorax without adhesions:

	Number	Per Cent
Able to work	33	70.2
Not able to work	1	2.1
Died from tuberculosis	11	23.4
Died from other causes	1	2.1
Unknown	1	2.1
Total	47	

Group 2.—Cases of complete pneumothorax but with localized extended adhesions:

	Number	Per Cent
Not able to work................	14	33.33
Died from tuberculosis	28	66.66
Total	42	

Group 3 (a).—Cases with incomplete pneumothorax on account of larger adhesions:

	Number	Per Cent
Able to work	5	11.1
Died from tuberculosis	39	86.7
Died from other causes	1	2.2
TOTAL	45	

Group 3 (b).—Cases with extensive adhesions. No pneumothorax practicable:

	Number	Per Cent
Able to work	9	11.8
Not able to work	3	3.9
Died from tuberculosis	63	81.8
Unknown	2	2.6
TOTAL	77	

The results obtained by Rist, of Paris, at the Laennec Hospital, were compiled in 1925 by Naveau, in a detailed monograph. Of cases of the common fibrocaseous form, 534 were treated. Of these, 48 per cent showed cures or improvement; 17 per cent remained stationary; 34 per cent became worse or died. The earlier the intervention, the younger the subject and the more complete the collapse, the better the results. The occurrence of fluid in 57 per cent of Rist's cases was regarded as only an incident and did not appear to vitally affect the results. Cures by pneumothorax appeared definite in 90 per cent of cases. The chief cause of failure was the spread to the better lung, an event particularly to be feared during the first eighteen months. Pneumothorax is compatible with pregnancy and in the majority of cases prevents a reactivation of disease. It has a good effect, but less definitely so, in pregnancy superimposed upon tuberculosis and in postpuerperal tuberculosis. The longer the treatment is continued the better the chance of cure.

Rist had among his group fifty-nine cases, twenty-six men and thirty-three women, who refused pneumothorax. Of this number 81 per cent died, most of them during the first year. This figure contrasts with 34 per cent of deaths in treated patients selected from the same category.

Intervention was attempted in all of the 756 cases, excluding a group of thirty-six pregnant women. Pneumothorax was accomplished in 583 cases and was unattainable in 167 of these on account of adhesions. Thus adhesions prevented collapse in about one case in five. Figures for men and women are about the same. Of the 167 thus deprived of pneumothorax eighty could be followed; fifty died or were worse, *i.e.*, 62 per cent; twelve were better, *i.e.*, only 15 per cent, as against 48 per cent of those treated.

Rist had a surprisingly small percentage of partial collapse—only 10 per cent. He has sought an explanation and finds it in the fact that his patients are collapsed with as little delay as possible. In checking his partial collapses against results, he finds that this group comprises 62 per cent of the stationary or unaffected cases. Statistical results reported by the Matsons in this country on 1004 cases and by Andrew Peters on 273 cases at the Loomis Sanatorium are essentially in accord with those given.

VARIETIES OF COLLAPSE IN ARTIFICIAL PNEUMOTHORAX

Most workers strive for a collapse as complete as possible and this is the generally accepted optimum.

A very interesting mode of procedure has been developed by Barlow and Kramer, "selective collapse," although the idea was advanced earlier by Morgan, of Cardiff, in 1912. Barlow and Kramer begin with the hypothesis that a complete collapse of the lung is undesirable. By giving frequent small refills the gas will localize over the site of greatest need and cause it to collapse, while the healthier lung tissue remains expanded. This method is said to reduce complications to a minimum, and throws much less strain on the heart and opposite lung. Hennel and Stivelmann arrive at the same results in another manner. They collapse the whole lung in the orthodox manner, then lower the pressure, affirming that the healthier lung tissue reëxpands while the diseased tissue remains collapsed. This collapse is supposed to maintain itself owing to a loss of elasticity in the diseased area. Both methods have their adherents. The Barlow-Kramer method is troublesome in the time required; it is applicable to only a few cases in which the diseased area is free from adhesions, and the method is difficult of control.

On the other hand, there are a few cases in which the selective collapse is quite striking and where it can be carried through very satisfactorily. It can be tried to advantage in bilateral lesions of not too great extent, the object being to attain a selective collapse on both sides such that there is no great strain upon the respiratory function. This simultaneous bilateral pneumothorax is to be distinguished from successive bilateral pneumothorax in which the collapse of one lung is followed by activation in the other lung, with abandonment of the first collapse in favor of that of the opposite side or a subsequent continuation of the two. Although a number of reports of excellent results with this treatment have been published, particularly in Italy, there have doubtless been many failures unreported. It should not be employed except by those skilled in the treatment and possessed of the soundest judgment.

DURATION OF TREATMENT

Many cases answer this question themselves. The occurrence of fluid may be followed by the formation of adhesions which often cause re-expansion of the lung; circumstances may be such that pneumothorax cannot be maintained, or the patient may weary of the treatment. In considering the ideal case, however, where such contingencies do not enter, the collapse should be continued at least two years and preferably longer. Many operators insist upon four years as a minimum and cite numerous patients who have persisted considerably longer. Here and there are "gas clinics" of men and women restored to normal working capacity, who prefer the slight inconvenience of a refill every three or four weeks to the risk of allowing the sick lung to reëxpand. Thus it will be seen that each case is a law unto itself. In general it may be stated that the longer the collapse is maintained the better will be the result.

SANATORIUM CARE

It seems scarcely necessary to state that sanatorium care should be carried out as far as possible in conjunction with any form of collapse therapy. Operative treatment is to be regarded only as a potent aid to the accepted, more conservative, measures.

EXTRAPLEURAL THORACOPLASTY

This procedure has already been briefly mentioned. As an operation it is too technical for more than a few words of description. For details the reader is referred to standard works, such as those of Sauerbruch, Lilienthal, and John Alexander's *Surgery of Pulmonary Tuberculosis*.

The operation is extrapleural and depends for its efficacy on the practically complete collapse of the chest wall. This statement suggests a very mutilating operation which, however, it is not. Under local anesthesia, which may have to be supplemented by slight general anesthesia, the whole operation is usually performed in two stages ten days to three weeks apart. Sections of the ribs of the affected side are removed posteriorly, a small section of the first rib and increasingly downward to the tenth, from which roughly 10 to 13 centimeters of bone are removed. Thus the excised bone area is roughly wedge-shaped. The curving incisions sweeping outward along the paravertebral line permit the laying back of the tissues to expose the ribs. Each rib is excised as close to its spinous process as possible, thus obtaining a straight inner line of rib resection, while the outer line is outward from above downward. The periosteum is elevated and the appropriate amount of rib removed. As the result of the two or possibly more stages the thoracic wall collapses down upon the vertebral column,

thus collapsing the lung. Bindings are applied to maintain the collapse until sufficient bone shall have regenerated from the intact periosteum to give a firm chest wall. The preservation of the shoulder-girdle obviates the drop of the shoulder. The small degree of chest deformity is rather astonishing and can be concealed, if necessary, by a pad.

Indications.—In theory one might say that any case suitable for pneumothorax, in which the latter method is impossible or unsatisfactory, becomes a candidate for thoracoplasty. However true this may be theoretically, it is certainly not applied in practice. The contralateral lung in thoracoplasty must be taken more into consideration; also other factors, such as the age of the patient and the natural tendency of the diseased lung to retract. From pneumothorax one can withdraw: from thoracoplasty there is no turning back. While the theory does not hold practically, the error is much more often on the side of withholding thoracoplasty than of applying it too frequently.

The chief indication lies in the unilateral case in which adhesions prevent any pneumothorax, and where there has been a considerable effort at retraction on the part of the diseased lung. The productive type of disease is favorable, whereas the exudative type is unfavorable. Archibald insists that the trachea be drawn over as evidence of lung retractability. The general condition of the patient must be considered. Operation should be avoided during extension of the disease, and periods of absolute or relative apyrexia selected. The heart and circulation must be carefully studied. When the better lung is open to question, Sauerbruch proposes a preliminary phrenicotomy on the diseased side, with the view that any tendency to activity on the better side will manifest itself and danger from this source appreciated before it is too late.

A second indication is found when pneumothorax is insufficient or its forced abandonment is followed by activity in the lung.

A third indication is tuberculous empyema of any form not yielding to other treatment. The best judgment here is none too good. Operation should not be delayed too long and not seldom excellent results are obtained.

Results.—The results from thoracoplasty, when considered in gross, are probably very misleading as to the real value of the operation. In its infancy the procedure was too often regarded as a desperate measure and by most surgeons was applied to cases who had exhausted other measures, most of their reserve strength and all other chance for recovery. That a total of 1,159 cases, gathered by John Alexander up to the publication of his monograph in 1925, should have shown 36.8 per cent of cures, seems the more remarkable. As subjects are better selected and technic improved this percentage will be much better. As evidence of this, Brunner reported 91 per cent of favorable results among thirty-five patients presenting the best indication for operation, and Stöcklin had

already reported 54.5 per cent of cures among forty-four cases similarly well selected. Operative death occurring within forty-eight hours of operation is relatively rare, only 1.5 per cent. Sauerbruch, who has by far the largest series of cases, had less than 1 per cent of deaths during the first eight days after operation. Causes of subsequent deaths are tuberculous pneumonia of either lung, cardiocirculatory failure, and sepsis from wound infection.

John Alexander concludes his article on thoracoplasty with two optimistic paragraphs. "Surgery has favorably influenced 61.2 per cent of patients reported as operated upon during seven years prior to 1925 and has actually cured 36.8 per cent of them. This is a remarkable record in view of the fact that scarcely one of these cases was expected to survive by continuing with artificial pneumothorax or sanatorium régime. All were in the far advanced stages of consumption, most of them had cavities, and many had bilateral active lesions. With few exceptions all had been in sanatoria for one or more years and had attempted artificial pneumothorax treatment. They were referred for operation by leading specialists in tuberculosis because the prognosis was considered hopeless without surgical intervention. Surgery was used as a last resort. In view of these facts the results shown are nothing short of marvelous.

"The extent to which these results can be bettered depends upon the widespread use of the improvements that are being made in operative technic and in preoperative and postoperative management, especially in the proper selection of patients for surgery. It is probable that in the future operations will be performed while the patients are in good general condition and where the lesions are almost entirely limited to one lung. It seems probable that the present percentage of unfavorable results will then decrease and the percentage of favorable results increase by from 10 to 25 per cent."

PHRENICOTOMY

This operation was originally proposed by Stuertz in Germany, in 1907. In 1913, Sauerbruch reported five cases. The object of the operation is to produce paralysis of the diaphragm on one side by removing a section of its phrenic nerve.

The phrenic nerve takes its origin from the third, fourth and fifth cervical roots; occasionally it receives additional fibers from the sixth, seventh and eighth cervical and the first thoracic root. The main trunk extends under cover of the sternocleidomastoid muscle obliquely across the scalenus anticus muscle, then beneath the subclavian vein and along the external surface of the pericardium to reach the diaphragm.

A fair proportion of individuals, 20 to 80 per cent according to different observers, shows an accessory phrenic nerve which rises from the fifth cervical root and sometimes, completely or in part, from the third.

fourth or sixth, according to Felix. It passes anterior to the subclavian vein into the thorax to join the main trunk between the first rib and the lung hilum. For details as to anomalies in the location of the main phrenic nerve and its accessory the reader is referred to special textbooks and the study of Matson and Plenk.

It is stated that the phrenic nerve supplies the entire motor innervation of the diaphragm. A number of the earlier operations showed no hemidiaphragm. With an understanding of the rôle of the accessory nerve and its removal the desired paralysis of the diaphragm was attained. For details of the simple phrenicotomy and the later, more radical, operation of Goetz and Felix, the latter known by the term exeresis, or avulsion, the reader is again referred to the textbook. In exeresis the phrenic nerve is avulsed in order to accomplish the removal of the accessory innervation as well as that of the main trunk.

Anatomical and physiological basis for the operation lies in the effect upon the hemidiaphragm, which is immobilized, becomes flaccid and moves only passively. Immobilization of itself eliminates the pumping action of the diaphragm and rests the diseased lung. Ascent of the paralyzed diaphragm by relieving traction in the overlying lung is a very essential element. The rise takes place slowly and may require six months to one year to reach its maximum. According to various observers, the difference between the dome heights on inspiration on the two sides varies from 5 to 12 centimeters. The ascent is due and is in proportion principally to the retractile force of the overlying diseased lung. This force is best illustrated in old sclerotic cases of tuberculosis where trachea, ribs, mediastinum, heart and diaphragm are all drawn markedly to the diseased side.

The rise of the diaphragm results in a surprising reduction in the cubic contents of the hemithorax, from $\frac{1}{6}$ to $\frac{1}{3}$ according to different opinions. The diseased lung is allowed to collapse in proportion as the content of the thorax is reduced.

It was first thought that the action of the ascending diaphragm could be only upon the lower lobe. It is now accepted that there is an effect upon the whole lung in the vertical diameter. More recently the operation is being applied more and more to upper lobe lesions as well as to lower because the results are almost if not quite as good. Also it was believed that knowledge of pleural adhesions of the lower lungs constituted a contra-indication, but even this contention seems open to question. The pumping action of the diaphragm must have its effect on the upper portion of the thorax and it is evident that its elimination should be beneficial.

The clinical effects of successful operation are a general improvement, a reduction of sputum, relief in many instances of distressing cough, and, according to some surgeons, a checking of hemoptysis. Furthermore, aboli-

tion of the respiratory function of the diaphragm lessens the spread of infection by aspiration.

There is no resulting disturbance of circulatory, respiratory, or abdominal organs. Cough and expectoration are easier instead of more difficult as would be expected. Dyspnea, following the operation, may be barely perceptible in the beginning but quickly disappears.

Indications.—Theoretically, the disease should be unilateral, but as phrenicotomy burdens the opposite lung only very little and very gradually, this condition is much less rigorously demanded. Lesions of the base afford an indication of choice. Excellent results are not rare, even with non-tuberculous bronchiectasis. It should be stated that the operation is usually only a partial measure and is not indicated where pneumothorax would better accomplish the result and where thoracoplasty is called for. Welles, of Saranac Lake, N. Y., is having a certain number of remarkable results with phrenicotomy alone. Usually the operation is employed to supplement pneumothorax or it may be used as a preliminary to thoracoplasty.

Results.—There are very few harmful effects even with exeresis. Baer performed 100 exeresis operations without mishap. Sauerbruch had 300 such operations with only one operative death.

Ultimate results are difficult to estimate since the operation is so often performed in conjunction with pneumothorax and thoracoplasty. Many cases improve, some remarkably, with phrenicotomy alone. Cures are reported even of moderately and advanced disease, but they are the exception. Discussion of them will be found in Alexander's monograph. The procedure is rapidly gaining new adherents.

INTRAPLEURAL PNEUMOLYSIS

A few narrow band adhesions often prevent an otherwise successful artificial pneumothorax from accomplishing its result. In 1913, Jacobaeus, of Stockholm, proposed to sear through the adhesions with a galvano-cautery. He has perfected a thoracoscope similar in principal to the cysto-scope. This is introduced between the ribs and enables the operator to view the pleural cavity while severing the adhesions with a cautery introduced in a trocar through another pleural space. The method has a considerable vogue in Europe but has only recently been employed in this country. The Matsons, of Portland, Ore., are using it, also Welles, of Saranac Lake, N. Y. The Matsons state that in one group of their partial collapse cases, comprising nearly one-third of those selected for pneumothorax, they found in about 20 per cent an unsatisfactory collapse of the lung and failure to close cavities due to the presence of bands, strings and folds of adhesions between the collapsed lung and chest wall. Approximately one-half of these may be converted into successful results by cauterization of

the adhesions. Of twenty-five cases which they attempted, eighteen were clinically and technically successful.

OLEOTHORAX

This particular form of treatment is an outgrowth of efforts to maintain a collapse of the lung by means of a slowly absorbing oil, thus to avoid the frequent refills with air. Various investigators have attempted this without any great success, but Bernou, of France, has proposed what is now known as "oleothorax," and a few French physicians have thus far been its chief proponents. Bernou recommends a pure paraffin oil, thin, neutral in reaction, anhydrous, of high viscosity, and gravity about 0.88. It is easily sterilized in an autoclave. The needles should be neither too large nor too small, in order to prevent expulsion through the pleural puncture into the skin with production of "paraffinoma," and at the same time to permit the injection of the viscid oil. To the paraffin oil is added gomenol, a French antiseptic oil, to 2 per cent.

The treatment is recommended: (1) in purulent effusions without perforation, (2) in pleuropulmonary perforation, and (3) to prevent the formation of early adhesions. In the first group the treatment appears to find its greatest usefulness, particularly in cases serious from the outset and with septic temperature.

The method is new and not universally accepted in France. Its chief proponent is Küss whose name in pneumothorax carries much weight.

CONCLUSION

Surgical measures in pulmonary tuberculosis have established themselves. While most physicians will never apply the methods themselves they should realize their possibilities and be in a position to offer their aid to suitable cases otherwise doomed to death or chronic invalidism.

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CHAPTER XIII

RECENT ADVANCES IN THE TREATMENT OF LEPROSY

Richard P. Strong

GENERAL CONSIDERATIONS

Since the last edition of this textbook a very large amount of work has been performed with reference to improved methods of treating leprosy, and an increasingly large number of lepers have been treated in various parts of the world. Such work has been carried out especially at our National Leper Asylum at Carville, La., in Hawaii, the Philippine Islands, India, Japan, and in parts of Africa and of South America. More favorable results in the treatment of leprosy have been reported in the past few years from a number of localities than ever before, and from these reports it would appear that much progress had been made in the treatment of this disease, and particularly in our understanding of the value of careful and complete treatment. Several observers at least now believe that we are in a far better position to deal with the problem of actually reducing this much dreaded disease by treatment than we have hitherto been.

CHAULMOOGRA OIL AND ITS DERIVATIVES

In the article written in 1923 upon the treatment of leprosy for this textbook, the use of chaulmoogra and hydnocarpus oils and their derivatives was discussed.

Oral Administration.—It was pointed out that chaulmoogra oil when administered orally frequently proved to be too nauseating in full doses to be of much value to the majority of patients. For this reason McCoy previously recommended for oral administration that the oil be given in gelatin capsules after meals, beginning with 5 minim (0.3 c.c.) doses. However, this frequently did not prevent nausea. Denney (1927) who has been impressed with the improvement in some cases of leprosy following oral administration of large doses of the crude oil at the National Leper Asylum at Carville, has attempted to increase the dose tolerated by the stomach by the use of the oil in specially formalized capsules. These capsules seem to be resistant to the gastric juices, and the oil, liberated in the intestine and not in the stomach, does not produce the

same nausea and vomiting as when given in ordinary capsules. Of 250 patients in the hospital, 154 were taking crude chaulmoogra oil, by mouth, a dosage ranging from 3 drops to 400 drops daily, according to the tolerance of the individual.

While not enough data have been collected to warrant final conclusions up to the time the report was made, nausea had not occurred in any of the cases taking the oil in these capsules, notwithstanding the fact that much larger doses were being given than could be tolerated in ordinary capsules. How much, if any, of the oil was lost to the patient by a passage of the unbroken capsule through the alimentary canal was not determined, but the reports indicated that this occurrence was infrequent. Denney points out that in Carville, as in many other institutions for the treatment of leprosy, crude chaulmoogra oil is held in much esteem by many of the patients, and regret is frequently expressed that they cannot tolerate larger doses. The formalized enteric capsules were being tried with the hope that maximum doses of the drug might be given to a large number of patients, and a fairer estimate obtained of the therapeutic value of the oil than has been previously possible on account of the limited tolerance so often exhibited. If nausea and vomiting can be eliminated, the oral route should permit of the administration of sixty or more times the amount of oil than it has been possible to give by the intramuscular injection of the ethyl esters.

Rogers (1928) points out also that now one can procure without difficulty hydnocarpus oils probably of greater therapeutic value than formerly, and in purer form, which contain more of the active hydnocarpic acid and less of the more insoluble and relatively inactive chaulmoogric acid and other adulterants. These oils are therefore less nauseating than cruder preparations. Rogers has also found that one 2 grain pill (0.13 gram) of sodium hydnocarpate may be given by mouth after meals, three times a day, and increased daily by one pill, until ten or twelve are taken each day, and that the digestion is less likely to be disturbed by this preparation than by the crude oil. He found that some patients were able to take as much as 40 grains (2.6 grams) in twenty pills daily with advantage.

Among the reported results from the oral use of chaulmoogra oil are those of Ralph Hopkins who found as the result of several years' patient trial that of eighty-two incipient cases, 17 per cent were reported cured, and 4 per cent more showed disappearance of the lesions, indicating definite therapeutic effects. However, of eighty-eight typically developed cases, none cleared up, and only 21 per cent improved.

Travers (1927) has reported further experience in the Chinese treatment of leprosy by oral administration of a powder consisting of Hydnocarpus anthelmintica seed, 3 parts; Cannabis indica, 1 part. Twice daily ½ dram was given, soon after food, for adults, and proportionately less

for children; the dose measured in a small aluminum cup, the mixture being made up fresh every week. He believed this mixture did not upset the stomach in any way. Of 275 cases under treatment for over three months, 218 or 79.2 per cent showed definite improvement. During 1924, thirty-one of the cases showing no remaining signs of leprosy were examined bacteriologically and nine were found to be negative. These cases had been under treatment for approximately one year. During the first eight months of 1925, of twenty-seven examined, fourteen were negative after approximately two years' treatment. In a later analysis of 200 of the cases, all bacteriologically positive on admission, 81 per cent were improved and 11.5 per cent negative after treatment of between one and two years. If febrile reactions occurred, the treatment was stopped for a time, such reactions being followed by improvement. In only 2 per cent did irritation of the kidneys ensue. The treatment proved to be very popular among all classes of patients, and occupied very little time, one-half hour for 350 cases, and only cost 3 pence per month per patient.

Wheatley has also employed practically this same method of treatment orally, his medication consisting of 1 part of Indian hemp seed and 3 parts of Hydnocarpus wightiana kernels. The preparation is known locally as "tai fong chee," and was given in daily doses of 10 to 30 grains. The tai fong chee treatment which had been given in 345 cases showed that 229 were improved, but none markedly so or entirely cleared of infection at the time the report was made.

Defillo has also treated leprosy orally in the Dominican Republic where he found that the addition of tannic acid enabled larger doses of chaulmoogra oil from the Taroktogenos seed to be taken orally without digestive trouble in the following prescription: Fluidextract of rhizophora mangle 20 grams, sassafras 5 grams, rubus 5 grams, glycerin pure 5 grams, essential oil of sassafras, 10 drops. Five drops of chaulmoogra oil are given twice daily after food, and immediately followed by 25 to 40 drops of the foregoing mixture, the oil being increased daily by 6 drops without increasing the dose of the mixture, until 50 to 100 drops of chaulmoogra are taken daily. The results in the treatment of the cases, which are most nodular, are said to be good.

Johansen has recently recommended (1928) as being less nauseating, the use of benzocain-chaulmoogra oil in the oral treatment of leprosy, as well as for intramuscular injection. The employment of this substance is discussed on page 187.

The Annual Report for 1928 of the Surgeon General of the United States Public Health Service states that benzocain with chaulmoogra oil is being used at the National Leper Home at Carville in oral administration to counteract the emetic effect and gastric irritation of the oil. This treatment is being continued with very satisfactory results. Nearly all the patients who were previously unable to take the crude chaulmoogra

oil by mouth are now taking it in this form with no complaint of gastric disturbances.

At Hawaii (1928) the ethyl esters of chaulmoogra oil have been administered orally in an emulsion with cod-liver oil in fifteen cases over a period of four months. None of these cases has shown any symptoms of gastro-intestinal irritation other than of occasional emesis immediately after taking the preparation. The dosage has been daily and, depending in part on the weight of the patient, has ranged from 0.5 c.c. to 2 c.c. of the esters. The tentative plan is to attempt to reach a dosage of 10 c.c. of the esters a week per 100 pounds of weight. Several patients have now reached this dosage without any disturbance or discomfort. This is of much importance when it is recalled that the administration of the esters must usually be continued for at least several years.

Administration by Injection.—Rogers' method consists of the injection of soluble sodium salts of the fatty acids of chaulmoogra oil. He recommended particularly the sodium gynocardate in the treatment of leprosy. He found that watery solutions of this preparation could be injected subcutaneously and intramuscularly with beneficial results. However, since the injections were usually rather painful, intravenous injections of a 3 per cent solution of this preparation were recommended and employed. Following these injections Rogers sometimes observed that in cases with considerable thickening of the tissues, indicating the presence of vast numbers of lepra bacilli, a day or two later, slight febrile general reactions occurred, accompanied by inflammatory swelling and softening of some of the lesions. Moreover, on making microscopical examination of smears of portions of the softened nodules, the remarkable phenomenon of the wholesale destruction of the lepra bacilli by a breaking up into small acid-fast granules, was demonstrated, and the absorption of the softened nodules gradually took place. Even in cases in which no such marked inflammatory reaction occurred, repeated examinations of nodules showed progressive breaking up and disappearance of the organisms until in some cases both the thickening of the tissues and the lepra bacilli completely disappeared, an apparent cure being brought about.

As the result of four and one-half years of work on fifty-one cases treated for six months and upwards, 41 per cent were apparently cured, and another 39 per cent greatly improved, only one advanced case being no better. Rogers, however, mentions that in this series of cases the lesions were not nearly as advanced as those seen usually in leper asylums, and that in fact none of a small series of late European cases, treated in this manner with less frequent injections, were completely cleared of their lesions.

Perkins also considered that the use of sodium salts of the chaulmoogra group of fatty acids constituted a more active form of treatment of leprosy when given by intravenous injections. However, he pointed out that the

gradual obstruction of the veins appeared to be the main reason against the extensive use of this preparation. Rogers holds that the sodium salts of chaulmoogra oil are more active for treatment than the ethyl esters. Muir (1927) likewise believes that a water soluble preparation such as this should furnish the most effective method of administration of the oil. However, he also found that sodium hydnocarpate when injected intravenously, very quickly caused blocking of the veins, so that the treatment had to be suspended for want of superficial veins in to which to inject. This vein blocking was found to be due to an endophlebitis of the injected veins, often 5 or 6 inches of the vessel beyond the site of injection becoming impervious. Sections of the obstructed veins showed the presence of considerable proliferation and swelling of the intima, narrowing or obliteration of the lumen, leading later to the reduction of the vein to a thin fibrous cord or to its complete disappearance. Muir also found that when sodium hydnocarpate was given subcutaneously, much pain was caused.

Many attempts have been made to forego these difficulties and Henry has prepared sodium salts of selected fractions of the fatty acids of Hydnocarpus wightiana, of low melting points, much the same as those originally used by Rogers in Calcutta. A 3 per cent solution of this preparation was said to be quite painless on intramuscular or subcutaneous injection, but still caused some blocking of the vein in patients susceptible to this action. On trying a 1 per cent solution, however, Rogers reported that doses up to 10 c.c. could be given repeatedly into one vein in patients who could not tolerate the 3 per cent by that method. Further, the weaker solution gave as good reactions and improvement as the stronger one, apparently because it was not precipitated at the site of injection with consequent irritation of the lining endothelium, but remained in active solution in the blood. Since, however, larger amounts of the drug in stronger solution for intravenous doses are evidently advisable in some cases, such as early ones, in cases of which there are large numbers of bacilli in the skin, or in those nearly cleared up, the difficulty can be overcome, according to Muir, in the following manner: A syringe with a central nozzle and double the capacity of the required dose (20 c.c.) is used, into which is sucked through the needle of fairly large bore the required dose of 2 to 8 c.c. of a 2 per cent solution of sodium hydnocarpate. A prominent vein is pierced with the needle, and blood about equal in quantity to double the amount of the solution to be administered is sucked up into the syringe which is held horizontally. By rotating the syringe on its long axis with the needle in the vein, the blood becomes gradually mixed with the solution and the whole is then injected. This mixture has the effect of preventing the coagulation of the blood, and though Muir has administered the drug in this way thousands of times, he has never yet noticed clotting, nor has any untoward symptom occurred which might be due to the injection of clots. He has given 3 per cent sodium hydnocarpate solutions

in this way ten or twelve times, and large doses of a 2 per cent solution over thirty times, into the same point in the same vein, without blocking of the vein occurring. He has also found that the sodium salts derived from a special fraction of Hydnocarpus wightiana, and also the sodium salts of Hydnocarpus anthelmintica and alpina, block the veins less than the salts from the whole Hydnocarpus wightiana oil. These salts also have less hemolytic power than that of Hydnocarpus wightiana. Muir has found that mixture of the Hydnocarpus wightiana oil with 4 per cent creosote is less painful for subcutaneous injections, and Wilson in Korea has used the Chinese Hydnocarpus anthelmintica oil in the same manner with very good results. Muir uses as a usual routine in Calcutta injections of pure Hydnocarpus wightiana oil in gradually increasing doses up to 10 c.c. by the subcutaneous infiltration method, and then gives sodium hydnocarpate intravenously in a 2 per cent solution by the blood-mixing method as described above. Alternation of intravenous sodium hydnocarpate with subcutaneous infiltration of hydnocarpus oil with creosote is advised chiefly because of the hemolytic effect of the former preparation. He seldom finds it expedient to go beyond 8 c.c. of a 2 per cent sodium hydnocarpate solution, as higher doses are apt to cause a feeling of giddiness.

Labernadic and Lafitte have also employed Muir's method of subcutaneous injections of pure Hydnocarpus wightiana oil with 4 per cent creosote during three months, given twice weekly in doses gradually increasing from 2 to 10 c.c. They had no severe reactions and have obtained encouraging results.

The new form of sodium hydnocarpate of Rogers has been recently placed on the market by Burroughs Wellcome & Co., under the name of "alepol." The drug is described as a selected fraction of the sodium salts of the total fatty acids of hydnocarpus oil. The selection of the lower melting point of the sodium salts is said to obviate to a considerable extent the old disadvantage of vein blocking which occurred when these compounds were injected intravenously. The alepol can be used intravenously and intramuscularly, and is issued in 25 gram bottles. About 700 doses can be made from 100 grams of the powder. Rogers points out that the cost of the drug is about one-twentieth of that of the ethyl esters and that its use is quite painless. In his last publication (1928) he states that many hundred cases are under this treatment in Africa and elsewhere with very promising results. It is recommended that the first dose should be 0.5 c.c., increased by 0.5 c.c. at each dose up to 5 or more c.c. as long as no febrile or local reaction occurs, the injections to be given twice a week. Following any reaction in the form of slight fever, swelling and softening of the skin lesions, or pain in the nerves, a week's rest should be given and the same dose repeated and only increased again when no reaction follows. Repeated slight reactions should be aimed at, which will result in gradual disappearance of the lesions and the lepra bacilli,

the breaking up of the latter setting free antigen with gradual production of immunity. As the drug is quickly absorbed and is active by intramuscular injections, Rogers believes its intravenous use should be limited to cases ceasing to react and improve further by the former method of use. He also believes that the ethyl esters and creosoted Hydnocarpus wightiana oil can be used in similar doses, and in cases ceasing to improve on any of these, he says that sodium morrhuate is sometimes effective. According to his experiences in very early cases, six months' treatment may sometimes suffice to clear up the lesions in a case, but in advanced cases two or more years may be required. Injections should be continued for at least six months in all cases after disappearance of all symptoms and of the bacilli, and the patients watched for several years for relapses.

Ethyl Esters of Chaulmoogra Oil

Since 1919, when Holman and Dean prepared and employed the ethyl esters of the fatty acids of chaulmoogra oil, separated by fractional crystallization, these preparations have been widely used in the treatment of leprosy, often with very favorable results. The ethyl esters have been given by intramuscular and intravenous injection, by inunction, and by the mouth, and in a number of leper institutions their use has become the method of choice. These esters may be put in glass-stoppered bottles or in ampules sterilized at 120° C. for one half hour, or in a water bath at 100° C. on three successive days. Antiseptics may also be added. In the Philippines, 0.5 per cent of iodin is added to the preparation and heated until it is brown, which lessens the irritating properties. Muir has preferred the addition of 4 per cent creosote to the ethyl esters. The preparation of the ethyl ester chaulmoogrates by the most effective methods requires the services of a chemist and a chemical laboratory, since the distillation of the esters must be accomplished at much reduced pressure. For institutions, however, which are not completely equipped, Muir and his associates have described a simple and economical process which can be carried out with most simple apparatus.

Engel-Bey has recently called attention to the value of the German preparation, "antileprol," a proprietary preparation manufactured by Bayer & Company, which he claims was the first manufactured preparation of the ethyl esters of chaulmoogra oil. He states that antileprol has been used successfully and extensively in many localities in different parts of the world. For injections of this preparation he recommends 1.5 to 2 c.c. given intravenously only once or twice a week, or 5 to 6 c.c. orally. The dose may be gradually increased if the patient shows sufficient toleration, but will probably often have to be discontinued from time to time. He claims that a great advantage in the use of antileprol is that it is a standard preparation and is the most efficient preparation of the

ethyl esters which has been obtained. Several other observers have recently reported upon the use of antileprol. Unna (1928) points out that antileprol has been used with good results since 1909 in the treatment of leprosy. Rangel (1927) has reported good results both from intramuscular and intravenous injections. He believes that the intravenous route is to be preferred, since it is free from risk, and the fear of emboli from injecting an oily substance of this nature into the veins has proved to be groundless. Also, pain and local reaction are avoided, and the amount introduced in the system can be accurately determined, whereas with intramuscular injections an uncertain proportion may remain unabsorbed.

Treuherz has also obtained good results from the use of antileprol Bayer, combined with 2 per cent tartar emetic solution intravenously. After four years' experience with this method of treatment he has found that from 0.1 to 0.3 c.c. of antileprol can be injected intravenously without symptoms. In girls of sixteen to twenty years of age, 0.4 c.c. produced coughing, and larger doses caused dyspnea and other distressing symptoms. In males over forty, from 0.8 to 1.2 c.c. can be injected every other day without serious trouble and with good effects. This may be alternated with 2 to 3 c.c. of a 2 per cent solution of tartar emetic, each being injected intravenously every fourth day.

Wade, who has had a wide experience with the disease in Culion, finds that the ethyl esters obtained from the true chaulmoogra oil, Taraktogenos kurzii, and from Hydnocarpus wightiana and anthelmintica oils have similar therapeutic effects. He advises that iodin, 0.5 per cent, should be added to the esters with subsequent heating, as this tends to neutralize the irritant effects, though the iodin has no apparent therapeutic effect of its own. The preparation, if properly made, consists of a moderately thick, dark brownish, oily fluid which can be easily injected through a No. 20 gauge syringe needle. Wade thinks that the addition of 10 per cent creosote may sometimes be slightly more effective, but it has not proven sufficiently advantageous for general use. According to the experience at Culion, the esters and the pure oil do not give very different results. However, the oil must be pure, and rancid oil is especially irritating. The oil has the advantage that it can be used apparently, though cautiously, in cases with nephritis, and other conditions in which the ethyl esters should be avoided. He believes, however, that the esters are more active and generally have brought about somewhat more rapid clinical improvement than the oil. The injections are made into the muscle, usually into the fleshy portions of the buttocks and the arms. The subcutaneous route is sometimes used, especially for the pure oil. Rogers' soluble preparations have been discontinued at Culion. When the lesions are few and localized, as in early cases or in those which have improved under treatment, it is often advantageous to give local injections (infiltration) directly into the lesions themselves, in addition to the regular intramus-

cular injections. For the standard treatment he recommends the use of chaulmoogra ethyl esters with 0.5 per cent iodin except when contra-indicated. When nephritis or tuberculosis is present, whole chaulmoogra oil may be employed provided the complication is slight and non-progressive, but the treatment must be cautious and the patient carefully watched.

For the injections, glass syringes which are easily cleaned and sterilized are preferred. A 10 c.c. size is most convenient. The needle should not be larger than that required to inject the drug used. With the esters, a No. 20 gauge is satisfactory. The injection of pure oil with this size needle is more laborious, but a No. 18 gauge needle is rather large for general use. In the intramuscular injections, preferably into the buttocks, care should be taken to avoid injecting into a vein. Before injecting, a pull should be made on the piston of the syringe to detect blood, and if blood is drawn, the needle should be withdrawn and reinserted at a different angle. The injection should be given usually not less than once a week, and when the condition of the patient warrants it, twice a week, at intervals of three and four days.

With reference to the dosage, it is recommended that this be commenced with 0.25 to 0.5 c.c., increasing by 0.5 c.c. every week till the maximum tolerated dose is reached. For the majority of cases, single doses of 4 to 5 c.c. of the esters, or the oil once a week, are usually tolerated for a long time. Larger doses eventually lead to interruption of the injections or reduction of dosage on account of the complaints of the patients of local and general symptoms. This ultimately results in the giving of smaller total amounts. He points out that patients undergoing routine medication register a variety of complaints, particularly when the larger doses are reached. The conditions complained of are particularly: (1) the immediate effects of the drug—choking and dizziness, which appear immediately after injection; (2) local effects in the lesions—induration and abscess formation; (3) general effects—fever and headache; (4) effects upon the respiratory system—cough, chest pain, chest oppression and hemoptysis, which may not necessarily depend upon pulmonary disease. The most common complaints made by the Culion patients are cough, chest oppression, fever, malaise, and weakness, in the order mentioned. Pulmonary tuberculosis is one of the chief contra-indications to the treatment. Doses of the oil large enough to affect the leprotic lesions in tuberculous cases are decidedly harmful. As intimated, active treatment is contra-indicated when acute or advanced chronic nephritis is present. If the kidney involvement is not marked, the purified oil may be tried. The treatment should also not be administered to anemic and debilitated individuals. Those with marked cutaneous lesions do not as a rule tolerate medication well. Proper attention to the food and exercise of the patient has been found to be quite as important as the drug itself. Choking, appearing immediately after an injection, may be so severe as to be alarming.

To relieve an attack the patient is given a drink of water and then made to lie down quietly. In very few cases the paroxysms of coughing may be so severe as to require a hypodermic injection of morphin and atropin. At the Leprosy Investigation Station in Hawaii in 1927-1928, the mixed ethyl esters of chaulmoogra oil, to which 0.5 per cent of iodin had been added previous to sterilization by autoclave, were also continued as a routine treatment, the injections being given intramuscularly into the buttocks. It was here found that hydnocarpus oil could be injected intramuscularly without causing the intense pain which occurred when chaulmoogra oil was used in this way.

Benzocain Chaulmoogra Oil.—Johansen, at Carville, La., in order to render intramuscular injections of chaulmoogra less painful, has employed a mixture, containing chaulmoogra oil, 90 parts; olive oil, 10 parts; and benzocain, 3 parts. Three grains of benzocain are added to 10 c.c. of olive oil and mixed with a stirring rod. This is then added to 90 c.c. of chaulmoogra oil previously warmed on a water bath to 70° C.; the whole mass is then agitated in a flask until all remaining crystals of benzocain are dissolved. The mixture is filtered through filter paper and then heated on a water bath at 100° C. for one hour. Benzocain goes into solution without increasing the volume of the finished mixture. The maximum average comfortably tolerated dose has been found to be a semiweekly injection of 5 c.c. into the deltoid regions, alternating with 8 c.c. into the buttocks, and this dosage was adopted as a routine. Certain muscular patients tolerated 15 c.c. twice weekly with no reported discomfort other than that to be expected from the size and pressure of this amount of oil. It is believed that the preparation has the advantage of not causing pain and of being rapidly absorbed. The Annual Report for 1928 of the Surgeon General of the United States Public Health Service states that at the close of the fiscal year, 160 patients were taking biweekly intramuscular injections of this preparation, and the majority of these patients showed satisfactory improvement.

THE IODID ANTIMONY TREATMENT

It is well known that the iodids, and especially potassium iodid, often produce a marked reaction in leprosy. A number of observers have considered this salt useful, especially in connection with the diagnosis of the infection, because it was found that the nasal catarrh produced by its use often facilitated the search for lepra bacilli in the nasal secretions. Some workers have regarded the apparent exacerbation of the disease, produced by the drug, as dangerous. Muir, however, considers that the reaction produced by potassium iodid is not necessarily harmful, and that the breaking down of leprous tissue caused by the administration of the drug, if the dosage is wisely regulated, may be one of the most beneficial

processes possible in the treatment of the disease. Potassium iodid does not, however, lend itself to use in mass treatment. It is advisable to begin with small doses and to gradually increase these according to the tolerance of the patient. Less than 1 grain may cause a febrile reaction which will last two or three weeks, while later on as the condition improves, such massive doses as 240 grains a day may be taken without reaction. Muir believes that potassium iodid is a most useful therapeutic agent in all stages of leprosy. In cases in which a considerable amount of leprous granulomatous tissue has been formed, the breaking down of this tissue by potassium iodid apparently induces a considerable degree of immunity, and these two factors, the breaking down of leprous tissue and immunity, combined, are in his experience more powerful therapeutic agents in leprosy than any others which he has seen. The reaction signs after injection of the iodid are the following: (1) swelling up and erythema of the existing lesions; (2) the appearance of fresh rose-colored nodules which are often painful; (3) fever, not always present; (4) marked acceleration of blood sedimentation; and (5) apparent granulation of lepra bacilli in the lesions. If rose-colored nodules appear and disappear again in a few days, the physician can press the treatment with some assurance, as their disappearance is a sign of immunity and when this is present the breaking up of granulomatous tissue and setting free of bacilli in the general circulation will not cause further dissemination of active disease, but a gradual healing up of the lesions. While the treatment may be suitable for all the stages and types of leprosy in many cases, the larger doses produce swelling of affected nerves and induce pain and tenderness in them. In the second and third stages of the disease, in which lepromatous tissue is abundant, even the smallest doses generally produce all five of the reactions referred to above. As severe and prolonged reactions may be caused by potassium iodid, Muir points out that we should have means of controlling such, and that the salts of several of the heavy metals have this effect. He has found that potassium antimony tartrate given in small doses of 0.02 gram intravenously, every second day, will control reactions, and that adrenalin, 3 minims of the 1 : 1000 solution in 30 minims of saline, given subcutaneously or intramuscularly, causes immediate cessation of nerve pain.[1] It is recommended that the treatment begin with 1 grain of potassium iodid a day and that the dose be increased daily by 1 grain until slight local or febrile reactions occur; the treatment should then be continued in the same doses. When the temperature falls below 99° F. and local reactions begin to subside, treatment is continued in the same doses which, however, are only given once or twice a week. The dose is increased only when no reaction occurs. If a reaction lasts more than three days, he gives 0.02 gram of potassium antimony tartrate in 2 c.c. saline intra-

[1] Green has also recorded the successful use of repeated injections of adrenalin or of ephedrin in the treatment of the leprous reaction.

venously, every second day, until the reaction has ceased. When the dose of potassium iodid reaches 20 grains it is increased by 5 grains at a time, instead of by 1 grain, and when 60 grains are reached, the dose is increased by 30 grains at a time up to 120 grains; when no reactions occur it is further increased to 240 grains. A dose of 240 grains is continued twice a week for three periods of one month, with a rest of one month between each course. The drug is given dissolved in one or two tumblers of water at bedtime, and it is recommended that an intermission should only be made if the patient feels very weak. Muir believes that the use of this drug may also be of considerable value in aiding diagnosis and to determine whether the patient has really been cured of the infection.

Leonard Rogers has also stated that he has been able to confirm the value of potassium iodid in clearing up the last signs in cases of leprosy nearly cured with alepol, and in confirming the cure of cases who had lost all signs of the disease.

Hoffmann believes that antimony is a useful drug in treating leprosy with chaulmoogra preparations. While he thinks that chaulmoogra ethyl esters are the more active remedy, the addition of antimony renders treatment more effective. In earlier years some observers have attributed to antimony, when given by intravenous injection in the form of a solution of tartar emetic, rapid improvement in the ulcerative lesions of leprosy. However, many others have observed no marked benefit from the drug.

Labernadie has recently discussed this question and concludes that colloidal antimony is not effective in the treatment of leprosy.

TREATMENT OF CASES WITH POSITIVE WASSERMANN REACTION

It is well known that a positive Wassermann reaction has been obtained in many cases of leprosy. Lloyd, Muir and Mitra believe that in many instances this positive Wassermann reaction is an indication of existing syphilitic infection, and they point out that such reactions often yield to antisyphilitic treatment. Muir has found that a number of leprosy patients with a positive Wassermann reaction improve rapidly on antisyphilitic treatment, and that hence a combined treatment for both affections is desirable. In the more advanced stages of leprosy approximately 50 per cent of the patients gave a positive Wassermann reaction. He, however, admits that some of the positive Wassermann reactions in leprosy are unaffected by antisyphilitic treatment.

For the treatment of Wassermann positive cases of leprosy he recommends the new mercuric preparation made by T. A. Henry of the Wellcome Research Laboratories, the chemical name of which is 2-myristoxymercuri 3-hydroxybenzaldehyd or "Hg 33" (Avenyl). It is easily soluble to the extent of 25 per cent in hydnocarpus oil, and is only slightly more

irritating subcutaneously than the oil alone. Thirty cases of leprosy with positive Wassermann reaction were treated in Calcutta with almost invariable improvement, but most marked in those cases where the Wassermann reaction became negative. No effect had been produced on the Wassermann reaction in these cases by long previous courses of hydnocarpus oil alone.

Muir states that it is the non-toxicity and the ease of administration of Hg 33 in hydnocarpus oil that renders it a safe and effective remedy in lepers showing a positive Wassermann reaction. However, in only about one-half of the cases which he treated with this preparation did the Wassermann reaction become negative.

Neo-Arsphenamin.—The Annual Report of the Surgeon General of the United States Public Health Service, for 1928, shows that at the Kalihi Hospital, Hawaii, during the year, twenty patients have been treated by intravenous injections of neo-arsphenamin, some concurrently, with intramuscular injections of esters, some by the intramuscular injection of sulpharsphenamin without the esters. Striking clinical improvement within eight to ten weeks after the initial administration has been obtained in cases without the administration of esters. There was no clinical evidence of syphilis in these cases. All have made improvement during their treatment, but this is true almost without exception among all patients admitted, regardless of their medicinal treatment.

Treatment with Preparations of Gold.—Attention has recently been called to treatment with certain gold preparations by Hoffmann, Kupfer, Paldrock, Eubanas, and Feldt. Hoffmann and Kupfer believe that krysolgan made by E. Schering of Berlin is of special value in the treatment of the eye lesions. It is given as in tuberculosis, the doses beginning with 0.001 gram and gradually increased up from 0.01 to 0.02 gram, injected every fourteenth day at first, and later every eighth day, with occasional intervals of a few weeks. Reactions occur as in tuberculosis but are not so severe. In some macular cases there is a numbness for a few hours. No local reaction occurs except after two to seven days in the lesions. The most important results are lessening of any inflammatory affection of the eyes, decreased pain, and photophobia. Episcleritis may disappear, and cloudiness of the cornea resolve. Lepromata gradually disappear and the pupils become clear again with improved vision. Lesions of the skin and mucous membranes may also improve. Paldrock, however, found that the sanocrysin treatment of nodular cases had no favorable effect.

Feldt (1928), in reviewing the subject, concludes that the various gold preparations which have been used for leprosy for some years, including aurocantha, gold potassium cyanate, krysolgan and solganol, act merely by stimulating the natural defensive processes of the body through the reticulo-endothelium, and thus excite the natural healing powers.

TREATMENT OF ULCERS

For the treatment of leprotic ulcers at Culion, one of the most effective remedies for local application has been found to be a 1 : 1000 to 1 : 2000 solution of basic fuchsin. This, Wade states, is practically painless and easy to apply. Mercurochrome, acriflavin, and potassium permanganate may also be used in the same dilutions. Bland salves as boric acid and zinc oxid ointments are often useful.

At Carville it has been found that ulcers responded almost invariably with beneficial results from ultraviolet ray treatment. Nerve pains have also been relieved with the ultraviolet ray treatment and diathermy.

Cruz, in 1928, however, did not obtain favorable results with ultraviolet rays. He treated thirty-four lepers with local exposure to ultraviolet rays from a quartz mercury vapor lamp while they were also receiving chaulmoogra ethyl esters for over a period of eleven months, with a total time exposure of from fifteen minutes to eighteen hours, and for from one minute to two hours at a time. In closed lesions only temporary erythema without benefit resulted. The trophic ulcers showed little or no reaction, and the leprotic ulcers showed only brief temporary improvement, after which all healing was as slow as with other methods of treatment.

RESULTS OF MODERN TREATMENT

It seems to be generally admitted by those who have had the widest experience in treating the disease recently that the most successful results have been obtained with chaulmoogra or hydnocarpus oils and their derivatives. Lara (1928), summarizing the results of the treatment of more than 5000 cases of leprosy with the chaulmoogra derivatives at Culion during five years and nine months of intensive treatment, from 1922 to September 1927, points out that 589 cases have been paroled or discharged. With thirty-nine other negative patients who died in the colony, and 257 still under observation, a total of 885, or approximately 16 per cent, apparent cures have been obtained in a large group of cases, mostly of advanced leprosy and originally bacteriologically positive, who have received systematic treatment for from six months to nearly six years. It appears that children up to ten years of age respond best to the treatment, adults over thirty years, only half as well, while adolescents and young adults under thirty years of age are the least favorable for treatment. Advanced cases usually require at least three years of treatment. Lara points out that it is not yet possible to speak of absolute cures with the chaulmoogra derivatives as the period of observation has not been sufficiently long and a considerable number of relapses or interruptions occur during the first eighteen months of the negative period. However, he believes that after two years the incidence of relapses is vry low, probably

not more than 5 per cent. The occurrence of a few relapses after two or more years is not, in Lara's opinion, sufficient reason for asserting, as some have done, that complete cure may not eventually take place.

Nicolas and Roxas-Pineda (1928) have treated seventy cases of leprosy in children of one year eight months to fifteen years of age. The duration of the lesions, which were bacteriologically positive, was from a few months to five years. All but three were treated with ethyl esters and other chaulmoogra preparations for from ten months to five years and six months, but mostly for not more than two years. Of thirty-six males, eighteen or 50 per cent, and of thirty females, twenty, or 58.8 per cent, are now reported negative. The average duration of treatment was two years five months for early cases, and four years for advanced cases.

According to the Annual Reports of the Surgeon General of the United States Public Health Service, for 1927 and 1928, in Hawaii, the deep intramuscular injection of the iodized esters of chaulmoogra oil weekly has been continued as the basic treatment.

Studies have been also made of all lepers admitted to the Kalihi Hospital, in Hawaii, from January 1, 1921, to December 31, 1925, with special reference to the subject of parole in treated cases. During the five years there were 486 admissions of whom 143, or 29.42 per cent, were paroled. Of these cases, 361 were bacteriologically positive on admission, and 15.23 per cent of these have been paroled. The report further shows that in many of the cases under treatment, the disease appears to be at a standstill, or, in other words, the carrier stage is reached. In 1928, thirty-three of the patients that had been previously paroled were readmitted as relapsed with recrudescence of the disease.

Denney (1927 and 1928), reporting upon the results obtained in the National Leper Home at Carville up to June 30, 1927, states that the results have been especially satisfactory and that an increasing number of patients have shown gratifying progress toward permanent arrestment of leprosy. During the year 1926, three patients were paroled from the hospital with their leprosy apparently arrested, and Denney states while no spectacular results have been obtained with either the oral administration of the crude oil or the intramuscular injection of its ethyl esters, it appears that definite improvement has followed in a sufficiently large percentage of cases to encourage the patients in the continuation of the treatment. In 1927, it is reported, there were 255 patients in the hospital, and during the year two patients in whom the leprosy was arrested were discharged on parole, and they were regarded as no longer a menace to public health. During 1928, eleven lepers who had been under treatment for from two to seven years were released probationally. At this hospital considerable improvement in contraction and deformities of the hands and feet was noted in the cases attending the clinic regularly for physiotherapy treatment.

In the treatment of smaller groups of patients several observers have not obtained such encouraging results. MacLeod (1928), who during the past two years has been using at the St. Gile's Homes for British Lepers, London, preparations such as chaulmoogra oil, hydnocarpus oil, sodium gynocardate, etc., by subcutaneous and intramuscular injections, thinks it advisable to keep an open mind with regard to the specific action of these remedies. In his hands while some patients held their own and improved in their general health, the others were unaffected or showed only temporary benefit, and in none could a cure in the scientific sense be claimed. He thought perhaps the arrest in some cases was due to the natural course of the disease rather than to any so-called specific medication, and that general hygienic principles were of more importance than drugs in increasing the resisting powers of the patients to the disease.

DeLangen (1928), in a review of the literature, shows that complete cures of leprosy have been reported by some observers in from 5 to 50 per cent of the cases. In DeLangen's experience, however, in 102 cases in the Leper Asylum in the Dutch East Indies, only 5 per cent of recoveries was obtained by the chaulmoogra ethyl ester treatment. Of eight early cases there were four cures, one of which relapsed but recovered again after further treatment. Of twenty-four more advanced cases, only one recovered and fifteen showed great improvement; while of sixty-two advanced serious cases, none was cured and only twenty-nine were improved.

Our Public Health Service does not consider that there is any specific of proven value in the treatment of leprosy, although chaulmoogra oil is used in the great majority of the cases. The report of Surgeon General Cumming of the United States Public Health Service, for 1928, contains the report of Surgeon McCoy, and points out that in the appraisal of the value of any form of treatment, as well as for administrative purposes in determining a proper period of quiescence or arrest before discharge of a patient who has suffered from leprosy, it is necessary to consider the length of time during which the disease may remain in an apparently clinically arrested condition before recrudescence. An indication of the probable length of this period is suggested by the study of the relapses of 100 patients released as quiescent or arrested cases during the period of 1919-1923 at Hawaii. All of these patients had received treatment regularly with the derivatives of chaulmoogra oil during their hospitalization, and spasmodically after their temporary release. The time of relapse is somewhat uncertain. However, 57 per cent were readmitted with recrudescences within three years from the date of their release; 28 per cent after three years and less than five years after release; and 15 per cent during the fifth year. The numbers which are readmitted for relapses after the fourth year from release will be influenced by the fact that those remaining quiescent for that length of time may be discharged as nonlepers, and official contact is not so close as during the period when they

are on temporary release. However, ten or approximately 17 per cent of sixty-three cases, carefully examined and discharged as non-lepers during the period of 1912-1920, have been readmitted as relapses up to the present date, or at least eight years after discharge. Thus, it is suggested that from 15 to 17 per cent of leprosy cases that have been paroled will relapse after five years of apparent quiescence.

From the data the writer has collected during the past few years, and observations made in a number of leper asylums in different parts of the world, it seems evident that the treatment of leprosy with chaulmoogra oil and its ethyl esters, while sometimes beneficial and often very efficacious, and by far the most favorable means of treatment yet discovered, is not by any means ideal, and there is still very great need for a more efficient preparation for the treatment of this disease. Evidence of this is seen in the new methods of treatment still being frequently introduced.

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CHAPTER XIV

SERUM TREATMENT OF ERYSIPELAS

Harold L. Amoss

First Period.—Stimulated by the results obtained with diphtheria antitoxin in the treatment of diphtheria, attempts have been made to apply the basic principles of serum therapy to other infectious diseases. Marmorek, in 1895, immunized animals with increasing doses of virulent streptococci and obtained serum for therapeutic use. Chantemesse administered Marmorek's serum subcutaneously in 501 adult patients with erysipelas, most of whom were in the acute stage. He observed that patients thus treated became subjectively improved and that the lesion lost the intense redness, swelling and tenderness. Scaling appeared promptly, and the patient's temperature diminished quickly and rarely endured for more than two or three days after treatment. Roger and Bulogueri reported the results of treatment in a large series of cases. But Lenhartz was disappointed by the results and was impressed by the frequency of serum complications. Thus the use of serum for the treatment of erysipelas was gradually discontinued.

But soon, in 1912, another serum was prepared by Aronson who developed a polyvalent serum from the immunization of horses by the subcutaneous injection of strains both directly from human sources and from those which had been passed through rabbits.

Stawski reported excellent results among thirty adults, by the use of Aronson's serum; but the incidence of serum-sickness was high.

In turn, Aronson's serum was supplanted by a polyvalent immune serum developed in the same manner by the Höchst Farbwerke in Frankfurt a/M. The new serum was used subcutaneously in repeated doses by Meyer and Ruppel and intravenously by Wetz who obtained satisfactory results in sixteen out of twenty-three adult cases. Jochmann's conservative opinion was that the general improvement following the administration was more constant than the effects on the local lesion.

Second Period.—During the period of the World War, the vaccine treatment gradually took the place of serum therapy. As the preparation of Marmorek's serum came just after the discovery of diphtheria antitoxin, so the second period of the serum treatment of erysipelas was stimulated by the advance in knowledge concerning hemolytic streptococcal infections, especially scarlet fever. The work of Dochez, Avery and Lancefield, and

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of Dick and Dick, in showing the relation of a group of hemolytic strep-
tococci to scarlet fever and the so-called toxin production of these organ-
isms, opened the way for the production of scarlet antiserum and its
application in the treatment of scarlet fever. In 1925, Goresco and Popesco
reported excellent results on the treatment of eighty cases of erysipelas
treated with a polyvalent antistreptococcic serum prepared by Cantacu-
zenes. Chen, 1925, recorded a beneficent action of scarlatina antitoxin,
in a case of scarlet fever complicated by erysipelas, and Schabetai, in
1927, used scarlet fever antiserum in the treatment of eleven cases of
erysipelas, with an apparent effect on the general condition and fever
but without effect on the lesion. There was no response in a patient treated
after the fifth day of the disease.

The application of the scarlet fever studies to the problem of ery-
sipelas was a natural sequence, especially as Tunnicliff, in 1920, had, as
a result of agglutination and absorption studies, suggested the existence
of a type-specific group of erysipelas streptococci. In 1924, Birkhaug
was assigned the problem and reported, from a study of thirty odd strains,
that 91.2 per cent of strains isolated from cases were agglutinated and
cross-absorbed with each of seven rabbit anti-erysipelas sera. These and
further observations on the effect of antiserum prepared by immunizing
rabbits, suggested the advisability of immunizing a larger animal. As
a donkey was available, immunization was begun with subcutaneous injec-
tions of living cultures of strains from human cases of erysipelas. The
course of immunization of this animal was continued at another clinic by
Birkhaug and a horse was substituted. After weekly intracutaneous injec-
tions of seven representative strains of erysipelas over a period of six
months, by Bliss, Hansen and Amoss, the serum was found to possess a
high agglutination-titer against a majority, but not all of the strains iso-
lated from cases of erysipelas.[1]

Results of Treatment.—Birkhaug, in 1926, reported sixty cases treated
outside of the hospital. Twenty of his patients were recorded as severely
ill. He called attention to the prompt detoxication, the "dramatic" drop
in the temperature and the pulse rate, and the rapid fading of the ery-
sipelas lesion in patients treated early in the disease. Doane treated twenty-
four patients with unconcentrated serum, with very good results in two.
In a patient in his series, treated with concentrated serum, there was no
apparent improvement. He concluded that in a certain group the serum
had no effect, that the best results were obtained in patients with marked
intoxication and albuminuria, but stated that virtually any foreign pro-
tein might bring about the same percentage of apparently beneficial

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[1] The precipitin reaction described by Lancefield has also been used for the selection
of the strains for immunization. This reaction, while present in rabbits after long im-
munization, has not been observed with horse anti-erysipelas serum.

results. Musser observed prompt amelioration of toxic symptoms, fall in temperature and rapid disappearance of the lesion in eleven cases treated with serum.

Symmers and Lewis, using Lederle's serum, treated 121 cases. Among the first six patients treated intravenously, one died with pulmonary edema apparently resulting from the injection. They, therefore, administered the antitoxin intramuscularly from then on. In comparing the results among 131 treated cases with over 15,000 non-treated cases in the same hospital, these authors feel that the period of hospitalization was reduced over 53 per cent by treatment. The mortality among the serum-treated group was 5 per cent; in a group of 107 cases not treated with serum, 11 per cent; and among 15,277 non-treated controls 10 per cent. No data on the duration of the disease in each patient before treatment or on the number having serum-sickness are given. The only complications recorded are subcutaneous abscesses, and it is stated that the antitoxin has no influence on the incidence of this complication and does not prevent recurrences. These authors are very enthusiastic over their results.

Platou, Schlutz and Collins compared the results of treatment by three methods; local applications, X-ray radiation, and erysipelas antiserum. There were 155 cases in the entire series. In the group treated with antiserum, the mortality was one-fourth of that in the other two groups, and the duration of the symptoms and of the local lesion very much less.

Allan reports similar results in forty-three serum-treated patients among 209 cases.

The most valuable report on the serum treatment of erysipelas was made by McCann, in 1928. This unbiased observer studied in the hospital a first series of fifty-one adult cases of which thirty received serum. The mortality among the serum-treated cases was 20 per cent and among the non-treated cases 19 per cent. Late treatment was evidently not the reason for the discouraging results as the twenty-four living patients received the injection on an average of 3.9 days after onset while the six patients who died were treated on an average of 3.5 days after onset. All patients received large doses. The following year, 1927-1928, he treated alternate cases with antiscarlatinal serum (twenty-one cases) for comparison with those (twenty-four cases) receiving anti-erysipelas serum. There were no deaths in these series possibly due to milder infection during that year. The average stay in the hospital of the antiscarlatina-treated cases was 19.7 days compared with 16.6 days in the anti-erysipelas-treated cases.

The crucial test of the efficacy of the serum is probably its application to erysipelas in children. Birkhaug treated thirty-six infants, two weeks to twenty-four months old, with a loss of five (14 per cent). He states

that recovery was prompt if the antitoxin in sufficient and repeated doses was administered in the first three days of the disease.

In striking contrast to these figures are those of McCann, from the same city, who treated fifteen children with anti-erysipelas serum, of which eight (53 per cent) died. Sufficient doses of serum were given, but the author states that "the later onset of treatment might have significance as a cause of greater mortality." McCann did not agree with Birkhaug's statement as to the value of skin-toxin tests as reliable indications of the need of further treatment.

McCann calls attention to the serious objections to previously published reports because of inadequate control, and concludes that, if erysipelas serum is of value, the evidence which he presents indicates that the antiscarlatinal serum which he used is likewise of value in the treatment of erysipelas.

Hansen-Prüss, in our clinic, has studied carefully the results in fifty-five cases treated in the hospital. There were, in addition, five cases of cellulitis treated with antiserum.

Fifteen of the patients were children, among whom erysipelas of the body was much more frequent than among the adults in the series.

The serum was administered in thirty-one cases within the third day of disease; in twelve within the fourth day and in twelve between the fourth and fifteenth day of disease.

Large doses of the serum were employed. For example, in the adults 100 c.c. of the unconcentrated serum were given intravenously and in addition from 40 to 80 c.c. of the concentrated serum, intramuscularly. In only two instances were immediate severe reactions observed following the intravenous injection of unconcentrated serum and these occurred in persons over fifty years of age, with signs of chronic cardiovascular disease.

As the intravenous injection of the concentrated serum produced a severe reaction in the first patient treated, no other injections of this preparation were made intravenously.

Effects of the Serum.—The most noticeable and beneficent effect of the serum was the prompt disappearance in most instances of the distressing subjective sensations such as headache, anorexia, chilly sensations, general feeling of ill-being, local pain and of delirium. In a few cases the whole picture was transformed in a few hours. A patient complaining of restlessness and of temporary delirium became quiet and coöperative within three hours after the intravenous injection. But such a quick response is unusual. In from six to twenty-four hours there was such a response in most of the cases. In two instances the patient appeared to be distinctly worse after treatment. The detoxicating effect was observed regardless of the duration of the disease before treatment or whether the local lesion was affected.

There was little effect on the temperature: in only four instances

did the temperature come to normal and remain so within four hours after treatment, and in only three children did it reach normal within forty-eight hours.

On the local lesion, there was, as a rule, no spectacular effect. In a few instances when treatment was instituted before the third day of the disease, in both adults and children, there was prompt subsidence of the lesion. In eleven out of thirty-nine adults, there was a complete check of the lesion, and in two others there was an extension of less than 2 centimeters during the next twenty-four hours. The average duration of the lesion after the administration of the serum was seventy-six hours. So constant was the prompt and definite diminution of tenderness following treatment in every case save two, regardless of the day of disease, that one cannot escape the conclusion of cause and effect. Moreover, in the cases in which the lesion continued to spread following treatment, the redness and edema were less intense than in the original lesion before treatment, and scaling was prompt.

Apparently leukocytosis was a function of the infection and was not influenced by the antiserum directly.

In cases uncomplicated by chronic nephritis there was a definite effect on the albuminuria.

Albuminuria was present in twenty-three out of thirty-nine cases among adults and in four out of fifteen children. In cases not complicated by chronic nephritis, the albumin, even in amounts of 7 grams per liter, and casts disappeared completely within thirty to forty-eight hours after treatment was instituted. Even in the presence of chronic nephritis, the albumin diminished more rapidly than could be accounted for by dilution resulting from increased fluid intake.

There is no evidence in this series that the serum prevents complications. Of the sixteen cases in which there were complications, the complication was discovered in nine before serum treatment was instituted. The search for and treatment of sinusitis is one of the most important points in this report. In several instances in which the signs of infection persisted longer than usual after serum treatment, sinusitis was discovered and there was prompt recovery after drainage. In two cases, cultures from the pus yielded *Staphylococcus aureus* in addition to hemolytic streptococci. Abscesses were present in seven cases. In five of these, staphylococci were found. Adenitis was present in every case; suppuration in only one.

There were in the fifty-five cases ten deaths (18 per cent). The deaths are described as follows: one in a woman, 65 years of age, recovered from erysipelas, died with *B. coli* bacteremia; one, male, 32 years of age, history of chronic nephritis, recovered from erysipelas, died in uremia; one died of staphylococcemia from cellulitis of the face; four children and two adults admitted with streptococcemia and one woman with

chronic hypertensive heart disease died suddenly while convalescent from erysipelas.

Problem.—Since the organisms are present in the lesion and at least 2 centimeters beyond the advancing edge, the problem of treatment is more complicated than in scarlet fever in which the organisms are localized in the tonsils, adenoid tissues or in a wound. In scarlet fever, the toxic substances are probably elaborated in a localized area and are distributed generally by the circulation. If, by the injection of antibodies, the toxic substances are neutralized as they are absorbed, beneficent results become apparent. But in scarlet fever the local lesion (*e.g.,* angina) does not respond to serum treatment as quickly as the rash fades. In erysipelas as in scarlet fever, it is evident from the prompt amelioration of the toxemic symptoms following serum treatment, that toxic substances are neutralized, but rarely the local lesion is modified so quickly. Thus, erysipelas corresponds more to the complications of scarlet fever. Blake and Trask, as well as Park, have shown that antiscarlatinal serum has no effect on the complications of scarlet fever.

The presence of organisms in advance of the actual lesion and the definite lag or time interval which occurs between the intracutaneous injection of toxic filtrate and the appearance of the actual erythema and edema, place beyond reasonable expectancy any hope of stopping immediately the spread of the local lesion.

In spite of the several reports grouping the *Streptococcus erysipelatis* into a sharply defined type, there is great doubt that this is true. In our laboratory, Bliss has shown that, if there be a group of erysipelas organisms, it is very broad and even overlaps other groups. Using the Lancefield precipitin method, she has shown further that streptococci from cases of facial erysipelas do not belong definitely to a circumscribed group. As the work progresses, organisms are isolated which have no precipitin relation to those which are being used in the immunization of horses for the production of the serum. Thus, her work confirms the clinical observations that the serum is not yet sufficiently broad in its valency to warrant complete acceptance for clinical use.

Obviously, there will be cases, as we have already seen, in which the serum does no good whatsoever and may even do harm by the production of distressing serum-sickness. But there is some hope in the fact that there is an apparent overlapping of some of the immune bodies. McCann states that, if anti-erysipelas serum is efficient, an antiscarlatinal serum which he used is equally good.

One may conclude that in a limited group of cases anti-erysipelas serum is of decisive benefit if given within the first three days and in sufficient dosage, and warrants further use. But in its present state one may not expect beneficent results in every case, and there are no means at present of predicting the usefulness of the serum in the individual case.

It thus becomes evident that before arriving at final conclusions, the serum itself must be improved.

In the evaluation of the results obtained by the intravenous injection of large amounts of anti-erysipelas serum, the non-specific effect of protein therapy must be kept in mind. Schmidt, in 1916, advocated non-specific therapy in erysipelas, and Turnheim, a year later, reported amazingly good results by the injection of milk in erysipelas cases. Reichenstein and Kraus, and R. Schmidt, reported similar results. Many other reports have appeared. The most comprehensive is that by Ahlswede who reviews 200 cases treated by non-specific therapy. The only answer to be given at present to the question of the non-specific effect of the horse serum is that in the cases to be reported by Hansen-Prüss there was apparently no enduring effect in the cases where the serum was not specific. Either there was a good result or none at all.

Finally, Francis, in an excellent study of the recovery in erysipelas, was able to demonstrate neutralizing antibody early in the acute stage, and concludes that there is no theoretical basis for antitoxin administration. Nevertheless, we have seen a sufficient number of excellent results to warrant our continuing its use. It is possible that, although neutralizing bodies are present even early, they are not in sufficient concentration. It has been shown by Glenny that so-called neutralized mixtures of toxin and antitoxin, when diluted, are toxic. Here is a sufficient theoretical basis for administering an excess of antitoxin. Moreover, the erysipelas antiserum is antibacterial, but whether this property is advantageous in its application to erysipelas is as yet problematical.

Practical Application.—The best results obtained thus far have been in those cases treated early. After testing for sensitivity, 80 to 100 c.c. of unconcentrated serum are given intravenously with an equal amount of isotonic salt solution. In addition, in severe cases, from 40 to 80 c.c. of the concentrated serum is given intramuscularly. The doses are repeated twelve to twenty hours later in severe cases. The concentrated serum should not be given intravenously. In young children, the concentrated serum is used intramuscularly (anesthetize with procain).

It is our custom to take the rectal temperature every two hours, force fluids, give the patient food, determine total amount of albumin for each twelve-hour period, record the white blood-count daily and finally, to apply cold compresses to the lesion during the first twelve hours to relieve pain. Abscesses should be drained early.

Every patient with facial erysipelas is examined for sinusitis, and, if present, the sinus is drained immediately. Cultures should be made.

Causes of Failure.—(1) Late administration; (2) insufficient dosage; (3) infecting organism not covered by the serum; (4) sinusitis; (5) double infection (streptococci and staphylococci); (6) abscess of septum; (7) adenitis; (8) abscess of eyelids, etc.

Recurrences of erysipelas occur, even under treatment, especially when the serum is not potent against the infecting organism. But serum-sickness may simulate very closely such recurrences, as the only evidences of serum-sickness may be fever and erythema and swelling of the site of the previous local lesion. The erythema is usually more dusky, the swelling is less marked and there is absence of tenderness. Among our cases such a lesion has appeared a week after treatment and four days after normal temperature and the complete fading of the local lesion, to endure for twelve hours and disappear.

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CHAPTER XV

THE SPECIFIC TREATMENT OF LOBAR PNEUMONIA

Russell L. Cecil

GENERAL CONSIDERATIONS

At the present time the specific treatment of lobar pneumonia may be said to be in a transitional stage. Fifteen years have passed since the publication of the first studies of Neufeld and of Cole on the therapeutic value of Type I antipneumococcus serum. During that time the method of preparing Type I serum and the product itself have undergone practically no change. The Hygienic Laboratory of the United States Public Health Service requires a standard potency for Type I serum. Most of the biological manufacturers supply a Type I antipneumococcus serum for the market, and the products of these various manufacturers are practically uniform. Furthermore, the method of administration is still the same as that recommended by Cole in his first publications, that is, 100 c.c. of serum every eight hours intravenously, until the temperature drops to normal or near normal. The chief departure from this regimen has been to omit the injection which should be given some time during the night. There is no doubt that this failure to give three full injections of serum every twenty-four hours accounts in part for the indifferent results obtained by some investigators with Type I serum.

During the last few years, chemists and bacteriologists have been developing methods of refining and concentrating antisera. Some of this knowledge has been put to a practical application in the preparation of antipneumonococcus serum, and the newer products have led not only to increased interest in the specific treatment of Type I pneumonia, but have been instrumental in the preparation of specific sera against the other types of pneumococcus. To be sure, the value of serum treatment in Type II, Type III and Type IV pneumonia has not yet been established, but evidence is accumulating (as we shall show) that concentrated Type II antipneumococcus serum has a distinct therapeutic value, and there is reason to hope that, with efforts now under way, an efficacious Type IV serum may soon be available.

Before discussing the specific treatment of pneumonia with the newer derivatives, it might be worth while to review briefly the treatment of Type I pneumonia with standard Type I antipneumococcus serum.

Type I antipneumococcus serum, as introduced by Cole and his co-workers, is prepared as follows:

Horses are immunized by injections first of dead and then of living cultures of Type I pneumococci. The serum of the horse is tested for its power to produce agglutination of pneumococci of this type, and also for its effectiveness in protecting mice against multiple lethal doses of the same organism. Cole used the so-called "mouse protection test" to determine the therapeutic power of Type I serum. The standard which he finally set for an accepted therapeutic serum was one in which the serum should be of such a strength that 0.2 c.c. would protect mice regularly against at least 0.1 c.c. of a pneumococcus Type I culture of such virulence that 0.0000001 c.c. of an eighteen-hour broth culture would kill a mouse within forty-eight hours. When the horse produces a serum of such potency, it is bled under aseptic conditions, and after the blood has clotted, the serum is removed and placed in bottles for use.

Cole advocates the use of Type I serum for only those patients whose sputum and blood have been found to contain pneumococcus Type I. These preliminary bacteriological examinations cause some loss of time, but Cole claims, and I think rightly, that patients with other types of pneumonia should not be treated with Type I serum.

The method of determining pneumococcus types as described by Dochez and Gillespie is now so familiar to all laboratory workers that a full description of the technic seems hardly necessary in a treatise of this kind.

Small amounts of washed sputum are emulsified and injected intravenously into a mouse. After eight to twenty-four hours, the contents of the mouse's peritoneum are washed out and suspended in sterile saline solution and agglutination tests are made with the various types of antipneumococcus serum. Other methods of typing pneumococci have been described by Krumwiede, Avery, and others, but the test with white mice still remains the method of choice.

If the sputum examination or blood culture shows pneumococcus Type I, Type I serum is indicated and is administered as follows:

In order to avoid anaphylactic accidents, the patient is first questioned for a history of previous injections of horse serum and also for a history of hay-fever or asthma, as persons having such symptoms are likely to be sensitive to various proteins including those in serum. In any event, an intradermal skin test is performed with a small tuberculin syringe, 0.02 c.c. of diluted horse serum being injected into the skin. If the reaction to the test is negative, the wheal produced by the injection of serum fades away rapidly. If sensitiveness does exist, a genuine urticarial wheal begins to develop, usually within five minutes, which may increase slowly in size up to that of a half-dollar. This lesion usually reaches its maximum within an hour, and then rapidly fades away.

Cole believes that all patients who are to receive antipneumococcus

serum should receive a "desensitizing" dose of serum subcutaneously six or eight hours before the first intravenous injection. The reason for this is that occasionally one sees a patient in whom the reaction to the skin test is negative and yet in whom, on the injection of large amounts of serum, symptoms of serum sensitiveness appear. It is, therefore, advisable to inject 1 c.c. of antipneumococcus serum subcutaneously, even though the reaction to the skin test is negative.

In the small percentage of patients who are found to be sensitive to horse serum, Cole advises a more thorough method of desensitization. This consists in giving small amounts of serum subcutaneously at half-hour intervals, doubling the size of the dose at each injection. After 25 c.c. of serum have been given by this method, larger doses, consisting of from 50 to 100 c.c., may be injected intravenously without fear of shock.

Type I serum is administered intravenously. The serum is usually allowed to run into the vein by gravity and should be injected slowly. Cole advises that the injection of the first 10 to 15 c.c. of serum should occupy from ten to fifteen minutes. During this period, one watches carefully for any change in the patient's appearance and for increased rapidity of the pulse, dyspnea, cyanosis or urticaria. If these symptoms appear, it is well to stop the injection of serum for a few minutes to see if the symptoms increase in severity. Usually, they disappear rapidly and the treatment can be resumed. Experience has shown that, if antipneumococcus serum is to be successful, it must be given in large doses. It is necessary to inject a sufficient amount of serum to produce a balance of protective antibodies in the patient's blood, such as those occurring during natural recovery from the disease; for it is largely this factor upon which recovery depends. An effective concentration of immune bodies can be obtained in the blood only after all the circulating soluble substance has been neutralized. Once a permanent balance of antibodies in the blood has been achieved, a fall in temperature and a noticeable improvement in the condition of the patient should soon follow. The amount of serum necessary will vary in each case. Cole recommends an initial dose of from 90 to 100 c.c. The frequency and size of the succeeding doses must be regulated largely by the effects obtained by those preceding, but in most cases the serum should be given every eight hours in doses of from 90 to 100 c.c. until the patient's temperature drops to $100°$ F., or less, and remains at that point. The patient should be under observation day and night and the treatment should be given by night as well as by day whenever necessary.

REACTIONS TO SERUM

Cole describes three types of reaction which may follow the injection of antipneumococcus serum: (1) a true anaphylactic reaction; (2) a thermal reaction, and (3) serum disease.

1. In persons who are sensitive to horse serum, a more or less severe asthmatic attack with dyspnea and flushing of the face may develop at once or within from fifteen to twenty minutes after the introduction of serum, followed by cyanosis, sweating, cough, anxiety and an urticarial rash. An anaphylactic reaction, unless extremely severe, is usually relieved by a hypodermic injection of from 0.5 to 1 c.c. of a 1 : 1,000 dilution of epinephrin. These reactions rarely occur, and Cole believes that if sensitive patients are properly desensitized, serious anaphylactic reactions will probably never occur.

2. Another type of reaction which may follow the intravenous injection of serum is the so-called thermal or foreign protein reaction. This comes on usually from thirty minutes to one hour after injection and is characterized by a chill, some cyanosis, and rapid rise in temperature of from one to three degrees, which is followed by an equally rapid fall to normal or even to subnormal. During the fall, there is commonly profuse perspiration. After the reaction, the patient usually feels much improved. Sometimes the temperature remains normal, but ordinarily it begins to rise again after a few hours. Cole does not believe that this reaction is of benefit to the patient and thinks it should be avoided if possible. Patients with this type of reaction need little treatment other than reassurance and the application of heat to the extremities.

3. Following the administration of horse serum, a group of symptoms frequently occurs which is referred to as serum sickness or serum disease. These symptoms usually make their appearance from seven to fourteen days after the administration of serum, and consist of fever, skin rashes, most frequently urticaria or erythema, edema of the skin, general adenopathy, and pain and swelling in the joints. The attack usually lasts from a few days to a week and may recur one or more times at intervals of a few days. Not all patients receiving serum show the symptoms. According to Cole, mild symptoms of serum disease appear in about one-half of the treated patients, severe symptoms rarely. The severe cases are more likely to occur in patients who receive large doses of serum.

RESULTS OF SERUM TREATMENT

The most striking effects of serum treatment in Type I pneumonia are usually seen after a so-called thermal reaction. Sometimes the clinical change after one of these shock reactions is spectacular, and the marked amelioration of symptoms presents the features of a natural crisis. In cases in which a thermal reaction does not occur, a change in the patient's condition may not be so marked. However, even when the chill is absent, the patient's mental condition is generally improved, the cyanosis becomes less, and the pulse rate falls. No doubt, in many cases this improvement is due to an actual sterilization of the blood. Cole thinks that, in addition

to its other effects, antipneumococcus serum may have a detoxifying effect.

In our experience, the most striking results in Type I serum therapy have been noted when serum was administered on the first or second day of the disease and the whole infection was aborted, the temperature dropping rapidly to normal. In such cases, the physical signs never become frank, and the patient is practically well in forty-eight to seventy-two hours.

Type I serum often produces a marked improvement in septic patients whose blood contains 50 to 100 colonies of pneumococcus Type I per c.c. by sterilizing the blood and thereby reducing the infection to a localized process. Cole believes that the administration of serum does not cause any change in the rate of resolution of the lung tissue already involved. When given early, however, there is no doubt that the serum prevents spread of the infection to healthy tissue. There is no evidence that serum diminishes the incidence of pneumococcal complications.

EFFECT OF SERUM ON MORTALITY RATE

In Cole's series of 195 patients with Type I pneumonia that were treated with serum, there was a mortality rate of only 9.2 per cent. In Type I cases, before serum treatment was commenced, the death rate had been from 25 to 30 per cent. According to these figures, therefore, the death rate for patients with Type I pneumonia was reduced two-thirds by the use of serum.

Since the original report of Cole, the largest group of cases of Type I pneumonia treated with antipneumococcus serum is that reported by Wadsworth, who, in 1924, reported 445 patients in New York State treated with a potent Type I serum prepared by the New York State Department of Health. When the cases studied in army camps were eliminated, there were 277 cases with fifty deaths, a death rate of 18 per cent. In 344 patients with Type I pneumonia who had not received serum, the death rate was only 19 per cent, a figure only slightly higher than that for the treated patients. Shortly after Wadsworth's article was published, Locke reported a detailed study of 145 cases of Type I pneumonia in which the patients were treated with serum, with a mortality rate of 17.2 per cent as compared with a mortality of 16.9 per cent in seventy untreated patients.

After reading the studies of Wadsworth and of Locke, one wonders why the results reported in their series of cases were so much less promising than those obtained by Cole. Wadsworth's patients were treated with a potent serum by various physicians, some of whom probably did not administer serum in sufficiently large doses. The most serious criticism that can be made of Wadsworth's study is that there is no record of how

the serum-treated cases were selected. Presumably, those who were very ill received serum; those who were not, went without. This would explain the high death rate in the treated cases and the comparatively low death rate in the untreated series.

In Locke's series, the last seventy-one cases treated were controlled by a group of seventy untreated cases. Locke's death rate for untreated cases of Type I pneumonia, like Wadsworth's, was quite low, only 16.9 per cent, as compared with a death rate of 32.6 per cent in an untreated series of 141 Type I pneumonias recently studied at Bellevue Hospital. With such a wide divergence in death rate for Type I pneumonia in different institutions, it is hard to evaluate exactly the benefit conferred by Type I serum.

THE EFFECT OF TYPE I ANTIPNEUMOCOCCUS SERUM IN EXPERIMENTAL TYPE I PNEUMONIA

It is not surprising that, in view of the results reported by Wadsworth and by Locke, the popularity of Type I serum has decreased considerably since its original introduction by Cole, and yet the low death rate obtained by Cole (9 per cent) is significant; furthermore, the results obtained with Type I serum in monkeys subjected to experimental Type I pneumonia are most convincing. Cecil and Blake found that Type I antipneumococcus serum has a highly specific therapeutic action on monkeys with experimental Type I pneumonia. To my mind the experiments on monkeys prove the therapeutic value of Type I serum more convincingly than any number of statistics.

Why has Type I serum not come into more general use in the treatment of patients with Type I pneumonia? Perhaps the most important obstacle to its use has been the difficulty in getting an early bacteriologic diagnosis. In many cases sputum is not obtainable until several days after the onset of the disease, and then, too often, at least twenty-four hours elapse before the laboratory makes its report. This means that treatment with serum is begun late in the disease when its therapeutic effect is not as striking as when administered early. Another objection to the general use of Type I serum is the fear of reaction, either anaphylactic or thermal. Still another reason for its lack of popularity is the technical difficulty connected with the proper administration of large doses of serum. Cole advises that the serum be diluted with an equal amount of saline solution, and this means that three times in every twenty-four hours the busy practitioner must inject 200 c.c. of diluted serum intravenously. Finally, a most important obstacle to its further use is the fact that many observers have not been able to duplicate the low mortality figures obtained at the Rockefeller Hospital. The reasons for this failure may be several: (1) Patients are not treated early enough; (2) the serum may not be suffi-

ciently potent; (3) the serum is given in too small doses; or (4) the serum is not given frequently enough.

Before passing on to a discussion of derivatives of serum, something should be said about Type II antipneumococcus serum. Theoretically, Type II serum should be just as effective as Type I serum, but in addition to the practical disadvantages encountered in the administration of Type I serum other problems arise in the serum treatment of Type II
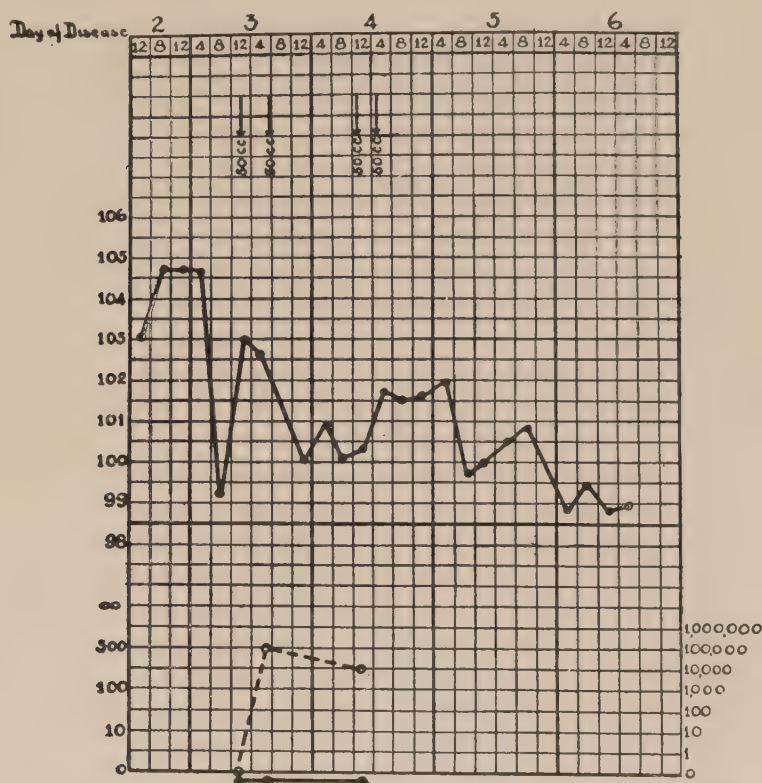
FIG. 1.—Pneumococcus Type II Pneumonia Treated with Type II Antipneumo-coccus Serum.

Dotted line shows prompt appearance of immune bodies in blood following injection of serum.

pneumonia. In the first place, it has been almost impossible to develop a serum equal in potency to that of a good Type I serum; in the second place, pneumococcus Type II, when growing in the body of an animal or man, produces much more specific soluble substance than pneumococcus Type I. In view of the ability of this substance to neutralize homologous serum, it is obvious that Type II infections will require a great many more antibodies than Type I infections. As a matter of fact, Cole and his coworkers at the Rockefeller Hospital tried Type II antipneumococcus

serum on patients with Type II pneumonia and were unable to demonstrate any therapeutic effect on the course of the diseases. During the winter of 1926, however, William H. Park, of the New York City Board of Health, immunized a horse against pneumococcus Type II and obtained a serum of such potency that 0.2 c.c. would protect a mouse against 0.2 c.c. of pneumococcus Type II culture; in other words, the potency of this serum was equivalent to that of the best Type I antipneumococcus serum.

Last winter my colleague, Baldwin, had an opportunity to test this serum on a number of patients with Type II pneumonia at Bellevue Hospital. Figure 1 shows the temperature, protection, and blood culture curves of a patient with Type II pneumonia, treated on the third day of the disease with Type II antipneumococcus serum. This patient had a sterile blood culture. One injection of serum was sufficient to establish a reserve of antibodies in the patient's blood. The patient received four other injections on the same day and two injections on the following day. The temperature came down at the beginning of the fifth day.

Examples of this kind led us to feel that in a certain number of patients with Type II pneumonia, in which treatment was begun early, the Type II serum exercised a definite therapeutic effect. Unfortunately, the number of patients treated was not sufficiently large to furnish reliable statistical evidence.

DERIVATIVES OF ANTIPNEUMOCOCCUS SERUM

In view of the obvious difficulties associated with the general use of antipneumococcus serum, it was natural that immunologists should make efforts to concentrate and purify the serum. Gay and Chickering were the first to show that the immune bodies in antipneumococcus serum could be removed by chemical methods. By mixing a solution of pneumococcus bodies with homologous antiserum, a voluminous precipitate resulted which contained practically all the immune substances of the serum. The immune substance contained in this precipitate was then extracted in a diluted alkaline solution at 42° C. The resulting water clear extract possessed the power to protect animals against pneumococcus infection, and it also contained other demonstrable antibodies, such as agglutinins and precipitins. By this method, a large proportion of the antibodies could be concentrated in a volume from one-fifth to one-tenth that of the original serum, but the product thus obtained was not stable, and the technic involved was so laborious that the authors considered the method impracticable for therapeutic purposes.

HUNTOON'S PNEUMOCOCCUS ANTIBODY SOLUTION

In 1921, Huntoon published a series of articles which depicted the removal of pneumococcus antibodies from antipneumococcus serum. The

method used by Huntoon was somewhat like that employed by Gay and Chickering, but in one respect fundamentally different. The precipitate obtained by Gay and Chickering was derived in great part from the serum proteins; hence, their solutions contained serum and gave serum reactions. Huntoon used only formed antigens which could be washed free from serum. This method eliminated to all practical purposes the serum constituents with the exception of the immune bodies themselves. Huntoon also introduced another innovation into the specific treatment of patients with pneumonia. His horses were inoculated against pneumococcus Types II and III, as well as against Type I. The serum was, therefore, trivalent, containing immune bodies against the three fixed types of pneumococcus.

The actual method of preparation of Huntoon's antibody solution is as follows:

Pneumococci of the three fixed types are exposed to the action of a large amount of an antipneumococcus immune serum, multivalent for Types I, II and III. The sensitized organisms are removed by centrifugalization, carrying the attached antibody with them. The bacteria are then washed free from serum by repeated changes of salt solution. Finally, they are emulsified in salt solution containing 0.24 per cent sodium bicarbonate and are heated to 55° C. for from thirty minutes to one hour. The emulsion is again centrifugalized, and the supernatant fluid removed, chilled, recentrifugalized and finally filtered through a filter candle.

Huntoon's antibody solution is a water clear product with a total nitrogen content of only 0.035 milligram per c.c. It gives a negative biuret reaction. Although no serum proteins are demonstrable by chemical means, they are detectable in a small amount by sensitization tests on guinea-pigs. Huntoon's antibody solution is stable when preserved at low temperatures.

Huntoon's antibody solution contains a fairly high content of protective bodies against pneumococcus Type I, 0.2 c.c. of antibody usually protecting against 0.1 c.c. of a virulent Type I culture. Its protective power against Types II and III pneumococci is not so marked. In many lots, 0.2 c.c. of antibody will protect against 0.01 c.c. of Type II culture, but even at this figure it is only one-tenth as potent for Type II as for Type I. Against Type III pneumococcus, the potency is even lower, the best lots rarely protecting against more than 0.001 c.c. of virulent Type III culture. It can readily be seen that, theoretically at least, Huntoon's solution possesses some advantages over the original antipneumococcus serum. Practically free from animal protein, it eliminates at once the danger of anaphylactic reactions and the discomforts of serum sickness. Furthermore, it contains some antibody against all three of the fixed types of pneumococcus and can therefore be employed at once without waiting for a bacteriologic examination of the sputum.

It seemed desirable to test the value of Huntoon's solution on experimental pneumonia in monkeys, just as we had previously tested Type I serum. Each of three monkeys received a lethal dose of Type I culture intratracheally, and promptly all developed symptoms and signs of pneumonia and septicemia. Seventy-two hours after infection, two of the monkeys received their first injection of Huntoon's antibody solution. The treatments were continued twice a day as long as either monkey showed symptoms. In both instances the injections quickly drove the pneumococci from the blood and, following this, effected a rapid recovery in both monkeys. The control monkey received no antibody and died on the fourth day of pneumonia and pneumococcus septicemia. From this experiment, it was clear that Huntoon's solution was just as efficacious in controlling Type I pneumonia as Type I serum had been.

Our next experiment concerned the treatment of experimental Type II pneumonia with Huntoon's solution. Eight monkeys were subjected to experimental Type II pneumonia by injecting a lethal dose of Type II pneumococcus culture intratracheally. Twenty-four hours after the injection the monkeys were sick. At this time, four of the monkeys were started on treatment with Huntoon's antibody solution, each monkey receiving 20 c.c. intravenously four or five times a day. Larger doses were used than in the case of Type I pneumonia for the reason that the antibody solution had less potency against Type II than against Type I pneumonia. The four monkeys that did not receive serum died of pneumonia and septicemia from three to five days after the infection. Two of the monkeys that received serum recovered and two died. In the two that recovered, the antibody solution appeared to have the same effect that it had had in the Type I infections, namely, it removed pneumococci from the blood stream; but it should be noted that this was not done in so striking a manner as in the Type I cases. In the other two monkeys treated, septicemia persisted in spite of treatment, and both died.

As Huntoon's solution contained some protective substance against Type III pneumonia, an experimental test was performed on monkeys with Type III pneumonia. Four monkeys were given a lethal dose of Type III culture intratracheally. All four promptly developed symptoms of pneumonia. Two of the monkeys were started on Huntoon's solution about seventy-two hours after injection. Three to five injections of antibody solution of from 10 to 20 c.c. each were given daily thereafter. In spite of this treatment, both monkeys died of pneumonia and septicemia, one on the seventh day and the other on the twelfth day of the disease. The control monkeys also died of pneumonia and septicemia.

From these experiments on monkeys, we were justified in concluding that Huntoon's polyvalent antibody solution was of great value in Type I pneumonia, of some value in Type II pneumonia and without value in Type III pneumonia. As will be shown presently, these results tallied

exactly with the results obtained in the treatment of patients with these types of pneumonia.

During the winters of 1920-1921 and 1921-1922, Huntoon's antibody solution was extensively tried out in the wards of Bellevue Hospital. In six medical wards, every patient with lobar pneumonia who was admitted, regardless of type, was treated with intravenous injections of antibody solution; in the other six wards, all cases of pneumonia were typed and the patients were carefully observed, but no antibody solution or other serum treatment was employed. Altogether, 424 patients with lobar pneumonia were studied in the antibody wards and 410 in the control wards. Practically all of the patients in the antibody wards received antibody, the only exceptions being a few patients who died or had their crises before antibody could be administered. The usual dose was 50 or 100 c.c. once or twice a day. Table I shows the results obtained (Cecil and Larsen). The most striking results, as in the monkeys, were observed in the Type I infections. In 158 cases in which the patients were treated with antibody, the death rate was only 13.3 per cent, while in 162 control cases there was a death rate of 22.2 per cent. In Type II infections, the figures were not so striking, but there was a difference. In eighty-three Type II cases, in which the patients were treated with antibody solution, the death rate was 27.7 per cent as compared with 40.3 per cent in the control wards. Patients with Type III infections were not benefited by antibody treatment, the death rate for the two groups being practically the same (39.7 per cent vs. 40.3 per cent).

One of the most interesting and unexpected features of this therapeutic experiment was the effect of Huntoon's solution on patients with Type IV pneumonia. One hundred and ten patients with Type IV pneumonia who were treated with antibody solution showed a death rate of 16.4 per cent, while 121 Type IV controls had a mortality of 24 per cent.

TABLE I—DEATH RATE IN PATIENTS TREATED WITH HUNTOON'S ANTIBODY SOLUTION COMPARED WITH DEATH RATE IN CONTROLS

Type of Pneumococcus	Antibody Wards			Control Wards		
	Cases	Deaths	Death Rate Per Cent	Cases	Deaths	Death Rate Per Cent
I	158	21	13.3	162	36	22.2
II	83	23	27.7	67	27	40.3
III	73	29	39.7	60	24	40.0
IV	110	18	16.4	121	29	24.0
Total pneumococcus	424	91	21.4	410	116	28.3
Streptococcus, etc.	48	24	50.0	35	12	34.3
Unclassified	36	14	38.8	47	20	42.5

TABLE II—DEATH RATES FOR PATIENTS WITH PNEUMOCOCCUS PNEUMONIA RECEIV-
ING ANTIBODY SOLUTION INTRAVENOUSLY WITHIN FORTY-EIGHT HOURS OF ONSET
OF THE DISEASE. CONTROL SHOWS DEATH RATE FOR PATIENTS WITH PNEUMO-
COCCUS PNEUMONIA ADMITTED TO CONTROL WARDS WITHIN FORTY-EIGHT HOURS
OF ONSET OF THE DISEASE

Type of Pneumococcus	Cases Treated with Anti-body			Control Cases		
	Cases	Deaths	Death Rate Per Cent	Cases	Deaths	Death Rate Per Cent
I	56	5	8.9	68	16	23.5
II	24	5	20.8	25	8	32.0
III	10	1	10.0	19	7	36.8
IV	24	4	16.6	45	11	24.4
TOTAL	114	15	13.1	157	42	26.7

When only those patients were counted who were treated early, more striking figures were obtained. In Table II the results for patients that were treated with antibody solution within forty-eight hours of the onset are compared with those for the controls who were admitted to the hospital within forty-eight hours of the onset of the disease. In fifty-six cases of early Type I pneumonia treated with antibody, the death rate was only 8.9 per cent; sixty-eight controls admitted early had a mortality of 23.5 per cent. The death rate for twenty-four patients with Type II pneumonia who were treated early was only 20.8 per cent as compared with 32 per cent in the controls. Even in the Type III group the treatment appeared to have some effect, but the number of cases was too small to furnish reliable information.

In addition to the investigations of Cecil and Larsen just reviewed, Conner has reported a series of 115 cases of lobar pneumonia treated by the intravenous injection of Huntoon's antibody solution. As in the report from Bellevue Hospital, the death rate for Type I, Type II and Type IV pneumonia appeared to be definitely reduced by the antibody treatment, while Type III infections showed no effect. In many instances Conner noted a striking influence on the clinical course of the disease following the injections.

The intravenous injection of Huntoon's antibody solution as originally prepared was practically always followed by a sharp thermal reaction from twenty to forty minutes after the injection. The patient began to shiver and soon had a sharp chill. There were cyanosis and dyspnea, and often considerable anxiety. The chill lasted from fifteen to thirty minutes. At its conclusion, the temperature showed a rise of two or three degrees, in rare instances even more. The high temperature usually persisted for

only a short time (from thirty to sixty minutes). After that, there was a rapid fall, accompanied by profuse perspiration. These foreign protein reactions usually followed each injection of antibody, but they tended to become less severe with each paroxysm. In three cases, the reaction following the injection of antibody appeared to be the immediate cause of death. In these patients, the symptoms were very severe: Chill, followed by high
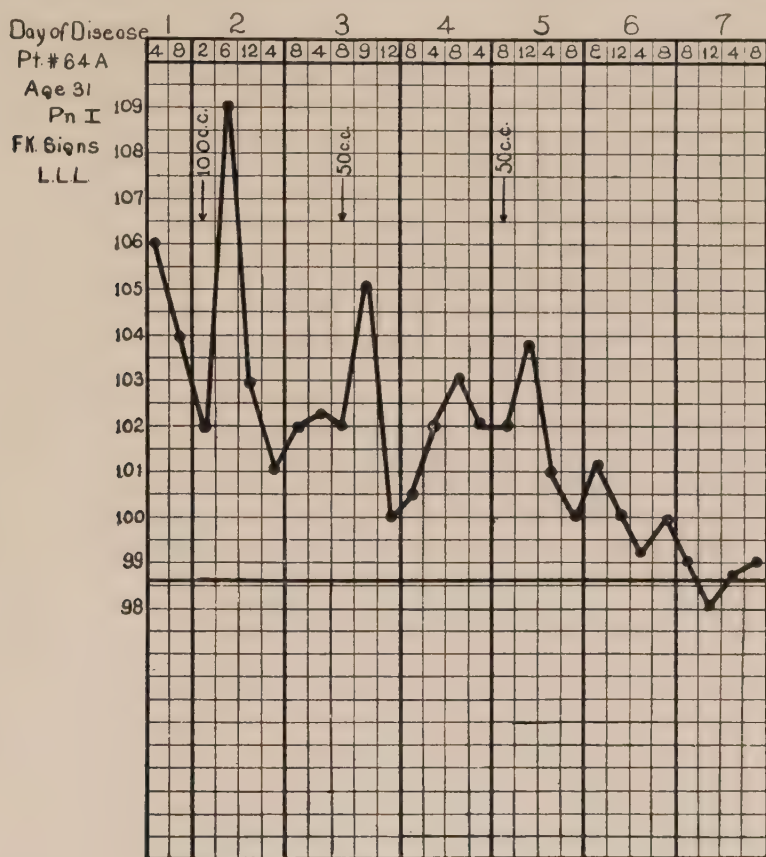
Fig. 2.—Pneumococcus Type I Pneumonia Treated with Huntoon's Antibody Solution.

Characteristic foreign protein reactions following each injection.

fever, delirium, cyanosis, dyspnea, rapid weak pulse, diaphoresis, congestion of the lungs, coma and death.

As one reviews this therapeutic experiment in the light of subsequent knowledge, it is obvious that we were obtaining something more than a purely specific effect. This is shown in the Type IV group in which the death rate was reduced to 16.4 per cent in treated patients as compared with 24 per cent in the untreated group. The specific antibodies contained

in Huntoon's solution must have played an important part in the reduction of the death rate in Types I and II pneumonia; but the sudden and spectacular termination of symptoms after some of the thermal reactions which followed the injections of antibody clearly indicates that the shock reaction itself was a therapeutic agent of considerable value in the treatment of these patients. In other words, the thermal reaction was a two-
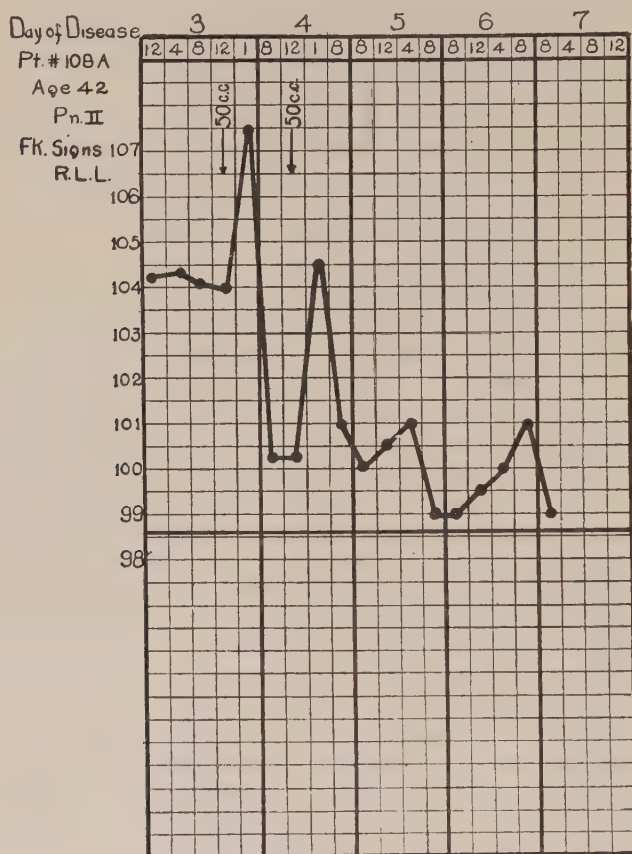
FIG. 3.—PNEUMOCOCCUS TYPE II PNEUMONIA TREATED WITH HUNTOON'S ANTIBODY SOLUTION.
Foreign protein reactions after each injection.

edged sword; it produced a brilliant therapeutic effect in some instances and was undoubtedly beneficial to the patient in most cases, but the occasional fatalities which occurred after this mode of treatment rendered it too dangerous a weapon to be used. If there had been some method of controlling the serum, we could have continued to make use of its beneficent qualities, but there was no way of telling whether a patient would react with a mild or with a severe chill.

Figure 2 shows the temperature of a patient with Type I pneumonia who had the characteristic thermal reactions. Treatment was started on the second day of the disease. Three intravenous injections were given and each was followed by a thermal reaction. Following the third reaction, the patient's temperature returned to normal and remained there.

Figure 3 shows the temperature of another patient treated with intravenous injections of antibody solution. This was a Type II infection in which the first injection of antibody was given on the third day of the disease. Two injections of the solution sufficed to bring the temperature down to normal and to effect a rapid recovery. The reactions following the
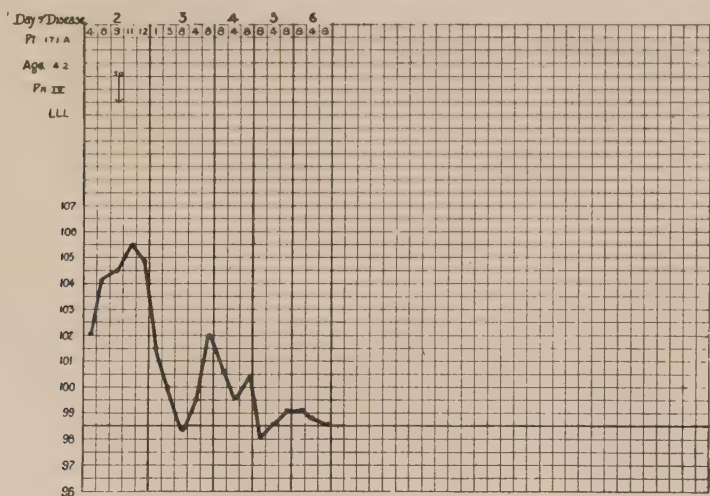
FIG. 4.—PNEUMOCOCCUS TYPE IV PNEUMONIA TREATED WITH HUNTOON'S ANTIBODY SOLUTION.
Sharp drop in temperature following one injection.

injections did not differ in any respect from those seen in the cases of Type I pneumonia.

In a few instances, Huntoon's solution appeared to have a striking clinical effect on patients with Type IV pneumonia. Figure 4 shows the temperature chart of a patient with Type IV pneumonia in which the intravenous injection of antibody produced a sharp reaction and apparently aborted the disease.

The next problem that presented itself was to obtain, if possible, the beneficial effect of Huntoon's solution without the disadvantages of the reactions. The simplest way to avoid the reactions was to inject the solution subcutaneously instead of intravenously. Larger doses of antibody were employed for the subcutaneous treatment, from 100 to 200 c.c. being the initial dose, and in severe cases even 300 c.c. was often given at one time. The average amount administered per case was 650 c.c. This method of administering antibody was tried in the wards of Bellevue Hospital

on alternate patients during the winters of 1922-1923 and 1923-1924. The results were rather disappointing. The subcutaneous method of treatment eliminated the chill, but appeared to have little effect on the course of the disease. The death rate for all types was almost as high for treated patients as for untreated controls. When only the early cases were compared, there appeared to be some difference. In Table III the death rate for patients with lobar pneumonia who received antibody subcutaneously within forty-eight hours after the onset of the disease are compared with that for patients with lobar pneumonia who were admitted to the control wards within forty-eight hours of the onset of the disease. There appears to have been some benefit conferred by the serum in Types I, II and IV, but the groups are small, and for that reason not altogether trustworthy.

TABLE III—DEATH RATES FOR ALL PATIENTS WITH PNEUMOCOCCUS PNEUMONIA RECEIVING ANTIBODY SOLUTION SUBCUTANEOUSLY WITHIN FORTY-EIGHT HOURS OF ONSET OF THE DISEASE. CONTROL SHOWS DEATH RATE FOR PATIENTS WITH PNEUMOCOCCUS PNEUMONIA ADMITTED TO CONTROL WARDS WITHIN FORTY-EIGHT HOURS OF ONSET OF THE DISEASE

Type of Pneumococcus	Cases Treated with Antibody			Control Cases		
	Cases	Deaths	Death Rate Per Cent	Cases	Deaths	Death Rate Per Cent
I	23	4	17.3	23	6	26.0
II	13	5	38.4	27	15	55.5
III	7	4	57.1	21	10	47.5
IV	40	7	17.5	28	8	25.0
TOTAL	83	20	24.0	99	39	39.2

Oliver and Stoller have also reported a series of cases of lobar pneumonia treated with Huntoon's solution subcutaneously. The results of this treatment were similar to those obtained by subcutaneous injections at Bellevue. The subcutaneous injections did not appear to sterilize the blood, and the effect on the death rate was not striking (17.3 per cent for twenty-three treated cases, as against 23.7 per cent for twenty-six controls).

In the meantime, Rhoades had made a study of the fate of pneumococcus protective antibodies when injected into normal animals and man. She found that, when pneumococcus antibodies are injected intravenously in a normal rabbit or man, protective bodies against pneumococcus Type I are readily demonstrable in the circulating blood immediately after the injection, and persist there for a variable period. On the other hand, she found that in animals injected subcutaneously with solutions of pneumo-

coccus antibody, a certain amount of protective substance was usually demonstrable in the blood, but that in some cases it did not make its appearance at all. The reason for this variation was not found.

Realizing the serious objection which the thermal reactions presented to the general use of pneumococcus antibody solution, Huntoon had been trying to eliminate the chill-producing substance from his extract; after considerable experimentation, he succeeded in removing the greater part of it without decreasing in any way the potency of his product. The antibody solution now obtainable in the market can usually be administered intravenously without causing a chill, particularly if doses of 50 c.c. are adhered to; large doses, from 100 to 150 c.c., are still apt to produce a chill, and, unfortunately, the large doses are often needed. Indeed, I doubt if the protective substance against Types II and III pneumococcus in small amounts of Huntoon's solution is sufficient to affect materially the course of a severe infection. If the dose is large enough to cause a chill, it may have a favorable effect not only on fixed types, but even on Type IV infections. When no chill is produced, the clinical effect is not striking.

Kessel and Hyman have recently reported fifty-six cases of pneumococcal pneumonia treated intravenously with Huntoon's antibody solution. There were nineteen deaths, a death rate of 33.9 per cent. These authors were not favorably impressed by the results obtained, but it is interesting to note that they were working with newer lots of the antibody solution which usually caused no chill after intravenous injection.

What Huntoon's antibody now needs is increased concentration. In a highly potent form it would doubtless be an excellent product for the specific treatment of patients with Type I or Type II pneumonia.

Felton's Concentrated Antipneumococcus Serum

In 1924, Felton published his first report on the isolation and concentration of the specific antibodies of antipneumococcus serum. In preliminary tests, Felton found that the protective substance was always associated with the water-insoluble fraction of serum, that is, the globulin. After various experiments, Felton found that the largest return of immune bodies could be obtained from antipneumococcus serum by simply diluting 1 part of serum in 10 parts of water. Taking advantage of this fact, he was able to isolate the specific antibodies and redissolve them in a concentrated form. The concentrate, of course, contained serum globulin in addition to the immune bodies. Actually these earlier lots of Felton's serum contained 3.5 milligrams of nitrogen per c.c. The technic employed by Felton was as follows:

One liter of serum is slowly poured into 15 liters of agitated, cooled distilled water, and the precipitate is allowed to settle over night in the

icebox. The supernatant fluid is then syphoned off, and the flocculent precipitate is washed with the same volume of cooled, distilled water used for the precipitation. The suspension is again permitted to settle for twenty-four hours. Once more, the supernatant liquid is syphoned off and the white sediment collected by means of a Sharpless centrifuge. The compact white residue in the bowl of the centrifuge is taken out and dissolved in one-half molecular sodium chlorid. If the solution is not clear, it is then passed through a Berkefeld candle. The resulting filtrate is a slightly opalescent fluid, free from sediment. By the use of this technic on a number of different antipneumococcus sera, concentrates two or three times stronger in immune bodies than the original were obtained. Even greater concentration, however, has been secured by using other solvents than sodium chlorid, such as tartaric acid.

One of our first experiments with Felton's serum was a test of its efficacy in the control of experimental lobar pneumonia in monkeys. The temperature, leukocyte and blood-culture curves of four monkeys that were infected with lethal doses of Type I pneumonia are shown in Figure 5. Twenty-four hours after infection, three of the monkeys were started on intravenous injections of Felton's Type I serum. The fourth monkey served as a control.

By referring to the charts, it will be seen that in the case of the three monkeys that received the serum, a striking effect was produced on the course of the disease. The temperature dropped and pneumococci disappeared from the blood, just as in previous experiments in which monkeys had been treated with Type I serum or with Huntoon's antibody solution. The three monkeys that were treated with Felton's serum made a complete recovery, while the control monkey developed a fulminating septicemia and died on the fourth day.

Felton has worked out a method of standardizing antipneumococcus serum in terms of a unit. Instead of using fixed amounts of serum against varying amount of pneumococcus culture, Felton titrates varying amounts of serum against a fixed amount of culture. The unit is that amount of serum necessary to protect a mouse against 0.05 c.c. of a 1 : 10 dilution of an eighteen-hour broth culture of pneumococcus, which is usually equivalent to at least one million lethal doses.

One of the first points to be determined was the relative potency of Felton's concentrated serum as compared with ordinary antipneumococcus serum. In order to settle this question, the following experiment was carried out on eight normal human subjects:

The blood of the eight individuals was first tested for protective power, four against pneumococcus Type I and four against pneumococcus Type II. None of the subjects showed specific protective bodies before the experiment. Two men then received *standard* Type I antipneumococcus
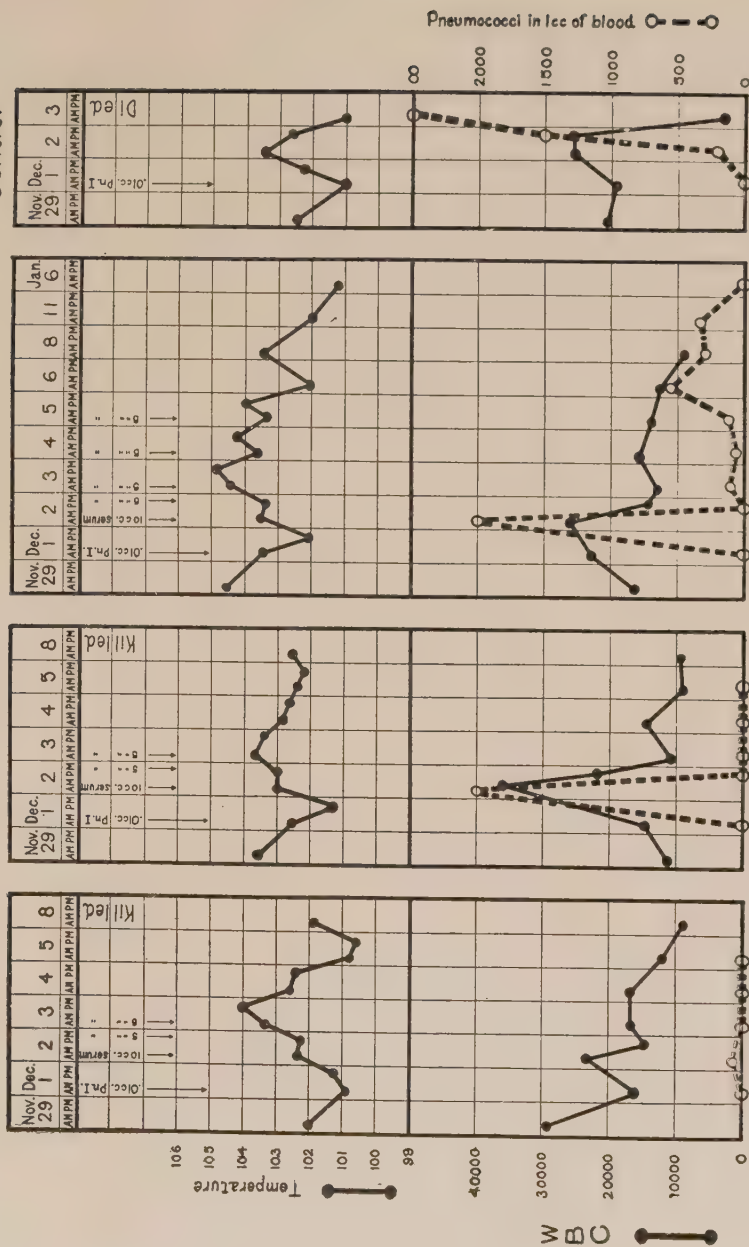
Fig. 5.—Temperature Charts of Four Monkeys with Experimental Pneumococcus Type I Pneumonia. First three treated with Felton's serum intravenously, with prompt recovery. The fourth received no serum and died on the third day. Dotted lines indicate degree of pneumococcus bacteriemia.

serum, the first subject 1 c.c. or 800 units, and the second 10 c.c. or 8000 units intravenously (Table IV). Two other men received 1 c.c. (2000 units) and 10 c.c. (20,000 units) respectively of *concentrated* Type I antipneumococcus serum. Thirty minutes after the injections, blood was taken from each individual for the determination of protective power.

TABLE IV—PROTECTION PRODUCED IN NORMAL HUMAN SUBJECTS BY IMMUNE SERUM AND BY REFINED IMMUNE SERUM

Pn. Type	1 c.c. Immune Serum	1 c.c. Refined Immune Serum	Ratio	10 c.c. Immune Serum	10 c.c. Refined Immune Serum	Ratio
Type I						
Potency of sera (units)	800 units	2000 units	1:2.5	8000 units	20,000 units	1:2.5
Protection in subject.	1,000 M.L.D.	10,000 M.L.D.	1:10	10,000 M.L.D.	100,000 M.L.D.	1:10
Type II						
Potency of sera (units)	320 units	800 units	1:2.5	3200 units	8000 units	1:2.5
Protection in subject.	100 M.L.D.	100,000 M.L.D.	1:100	10,000 M.L.D.	1,000,000 M.L.D.	1:100

In Table IV it will be noted that the subject who received the refined Type I serum showed considerably higher protection than that of the man injected with ordinary antipneumococcus serum. This was also true when a similar comparison was made between a standard Type II serum and a refined Type II serum (Table IV). Of course these tests are only a rough measure of potency, but they show clearly that both Type I and Type II refined sera are more potent than the unrefined (standard) antipneumococcus sera.

The high potency of Felton's serum, as compared with ordinary antipneumococcus serum, is well brought out by some comparative tests on rabbits recently conducted by Goodner. In testing the therapeutic value of seven different Type I antipneumococcus sera on rabbits infected subcutaneously with pneumococcus Type I, Goodner found that the minimal effective dose of serum necessary to bring about recovery in the rabbits was considerably smaller for Felton's serum than for any of the other sera tested. It is interesting to note that in Goodner's experiments, the therapeutic value of the serum did not always run parallel to the mouse protective value, but did check fairly well with its agglutinin titer. Excepting one particularly strong serum, Felton's concentrated serum was approximately fifteen to twenty times more potent in therapeutic value than any of the other sera tested.

For the past two years our work in Bellevue Hospital on the specific

therapy of pneumonia has been conducted almost entirely with Felton's concentrated antipneumococcus serum. Instead of treating patients in alternate wards, however, we have treated alternate cases in every ward. Treatment was administered as follows:

In every patient with an even number, treatment was instituted promptly with polyvalent serum. If sputum was obtainable, it was sent at once to the laboratory for typing, but as the type determination usually took from twelve to eighteen hours, it was deemed advisable to start treatment with polyvalent serum without waiting for the laboratory report on pneumococcus type. Patients with odd numbers received no serum of any kind, but in other respects were treated in the same way as the patients who received serum.

In order to avoid anaphylactic accidents, each patient was first questioned as to previous injections of horse serum and as to hay-fever, asthma or hives. An intradermal and an ophthalmic test were then made with a 1 : 10 dilution of normal horse serum. If after fifteen minutes these tests were both negative, 5 c.c. of concentrated serum were slowly injected intravenously. The rule was to devote five minutes to the injection of 5 c.c. of serum. If the patient showed no reaction to this first injection of serum, a second injection of 15 or 20 c.c. was given intravenously one to two hours later, and this dose was repeated in another two to three hours. An effort was made to inject from 75 to 100 c.c. of serum during the first twenty-four hours. One hundred c.c. was generally equivalent to at least 100,000 units against Type I, and to an almost equal number against Type II. The potency of the polyvalent serum against Type III has been either nil or so low as to be of comparatively small practical value.

The amount of serum administered on the following day was determined by the clinical condition of the patient. If his general condition had improved and if the temperature chart showed a decided drop in fever, pulse rate and respiration rate, the amount of serum administered was usually considerably less than that administered on the first day, that is, two or three 20 c.c. injections instead of four or five as on the previous day. If, on the other hand, the patient's condition was worse, or if it remained unchanged, the intensive treatment was continued. On the third day the same policy was pursued. If the patient's temperature was under 100° F. and his condition good, the general rule was to give one or possibly two of the 20 c.c. injections. If he remained ill, the intensive treatment was continued until crisis or death occurred.

Of the 441 cases who had received even numbers, 396 actually received serum. The discrepancy is due chiefly to the fact that for a certain period in the first year of the experiment, Type III and the miscellaneous group IV cases were not treated with serum, although they fell in the treated series. The great majority of the cases (75.8 per cent) for which potent serum was available, received an adequate amount, as measured in units of pro-

tective power. Type II cases received a smaller number of units than Type I cases, due to the lower potency of Type II serum.

Reactions.—Two types of reactions have been noticed after the intravenous injection of concentrated serum: thermal and allergic. Thermal reactions have been comparatively rare. Of the patients who received concentrated serum, 15.4 per cent have had one or more chills, but nearly all of these occurred after the use of certain lots. Some lots have never given a thermal reaction. The chills have nearly always been of a mild type, and never appeared to have any injurious effect on the patient.

The allergic reactions have nearly always occurred after the first intravenous injection of 5 c.c. or less of serum. In a few patients who had already received several doses of serum, a reaction occurred when 20 c.c. of a new lot of serum was administered (two cases), or when the dose of serum was sharply increased above the amount of the previous injection (two cases). The immediate allergic type of reaction manifested itself in the following way: From three to fifteen minutes after the injection of serum the patient's face became flushed, the respiration rate more rapid and the dyspnea more marked. The severe cases showed some cyanosis. The expression was anxious and occasionally the patient complained of precordial pain. Every one of these patients developed a simultaneous urticaria. One-third of the allergic reactions manifested themselves as urticaria without any other symptoms. During the winter of 1926-1927 the incidence of immediate allergic reactions was 10.2 per cent. During the winter of 1927-1928 the incidence was 3.9 per cent, and most of these latter reactions followed the use of sera prepared in 1926-1927. This suggests that many of the apparently allergic reactions may have been due to a substance in the serum capable in itself of exciting a reaction in a non-sensitive individual.

None of the patients who had anaphylactic symptoms died during the attack. One patient who was already quite ill with pneumonia died seven hours after an anaphylactic reaction and, naturally, the question was raised whether the reaction had been a factor in the unfavorable termination. In almost every instance the prompt administration of adrenalin subcutaneously relieved the patient of his unpleasant symptoms in the course of a few minutes.

Serum sickness developed in fifty-two or 18.8 per cent of the treated patients as compared with approximately 50 per cent of patients treated with standard antipneumococcus serum. The likelihood of a patient's developing serum sickness seemed to depend in great measure upon the amount of refined serum administered. Among patients receiving 50 c.c. of refined serum or less, serum sickness occurred in five cases or 4.9 per cent, while in those who received more than 50 c.c. of the refined product, serum sickness occurred in forty-seven cases or 27.2 per cent.

Results of Treatment with Refined Serum.—The results of any therapeutic agent in the treatment of lobar pneumonia have to be determined by its clinical effect on the course of the disease and its influence on the death rate. In the 441 cases of lobar pneumonia which comprise the treated series, there are many charts which demonstrate in a striking way the clinical effect of concentrated serum on the course of the disease. This applies particularly to the Type I group, but is true to a less extent of Type II infections. The best examples of immediate clinical effects were seen in those patients who were treated with serum on the first, second or third day of the disease.

From a large group of Type I and Type II cases that showed a definite change in their condition following the administration of serum, we have selected the following illustrations:

J. M., aged eighteen years (Fig. 6), Type I pneumonia, with positive blood culture. Treated with concentrated antipneumococcus serum on the first day of his disease. The response to serum was quick and permanent.

W. B., aged forty years (Fig. 7), pneumococcus Type II pneumonia, was admitted to the hospital on the first day of his disease. Treatment was begun twenty-four hours later, when his blood culture was weakly positive. No further observations were made of blood culture or protective bodies in this patient, but the marked and prompt change in his general condition and fall in temperature were quite striking.

Summarizing the clinical effects of concentrated serum, it may be stated that the administration of serum early in the course of the disease frequently causes a striking drop in the temperature and a general amelioration of the patient's symptoms. In the cases of Type I pneumonia treated within three days after onset, and Type II pneumonia treated within two days after onset, this is the rule rather than the exception. In cases treated later than this, the clinical effect is not always evident. If, however, the particular lot of serum used is highly potent in Type I or Type II antibodies, the clinical effects even in cases admitted on the fourth or fifth day of the disease may be quite impressive. In patients with pneumococci in the blood (pneumococcus Type I or Type II) the early administration of serum usually causes an immediate disappearance of pneumococci from the blood stream provided the sepsis is not extreme.

As pointed out above, all the cases of lobar pneumonia included in this series received a number as soon as the diagnosis of lobar pneumonia was made. Patients with even numbers received serum. Those with odd number received none. This method of assorting cases left their selection as treated or untreated entirely to chance. The method produced comparative groups that are surprisingly similar in all essential respects. In the first place the number of cases falling into the various types, both treated and untreated, was approximately the same. Furthermore, the figures were

analyzed with regard to various other factors which might have influenced the death rate. These factors were: (1) Day of admission to the hospital; (2) age; (3) complicating systemic disease, and (4) history of excessive
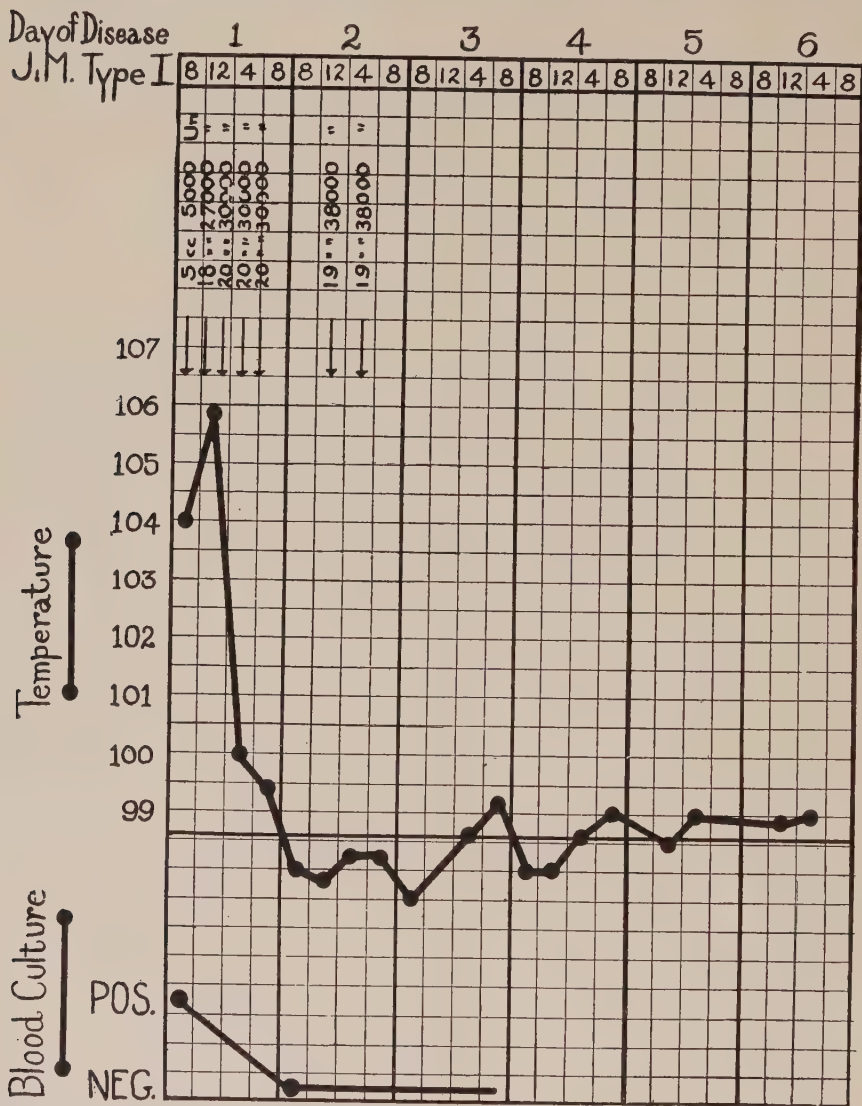
Fig. 6.—Pneumococcus Type I Pneumonia with Positive Blood Culture, Treated with Concentrated Antipneumococcus Serum on First Day of Disease. Quick and permanent response to serum.

alcoholism. Regarding these factors in the Type I and Type II groups, the distribution of cases in both the treated and untreated series was remarkably similar. In the comparatively small number of Type III cases,

the treated series contained twice as many instances of systemic disease as the untreated series. The miscellaneous Type IV series was less evenly selected than Type I and Type II in regard to three of the factors—
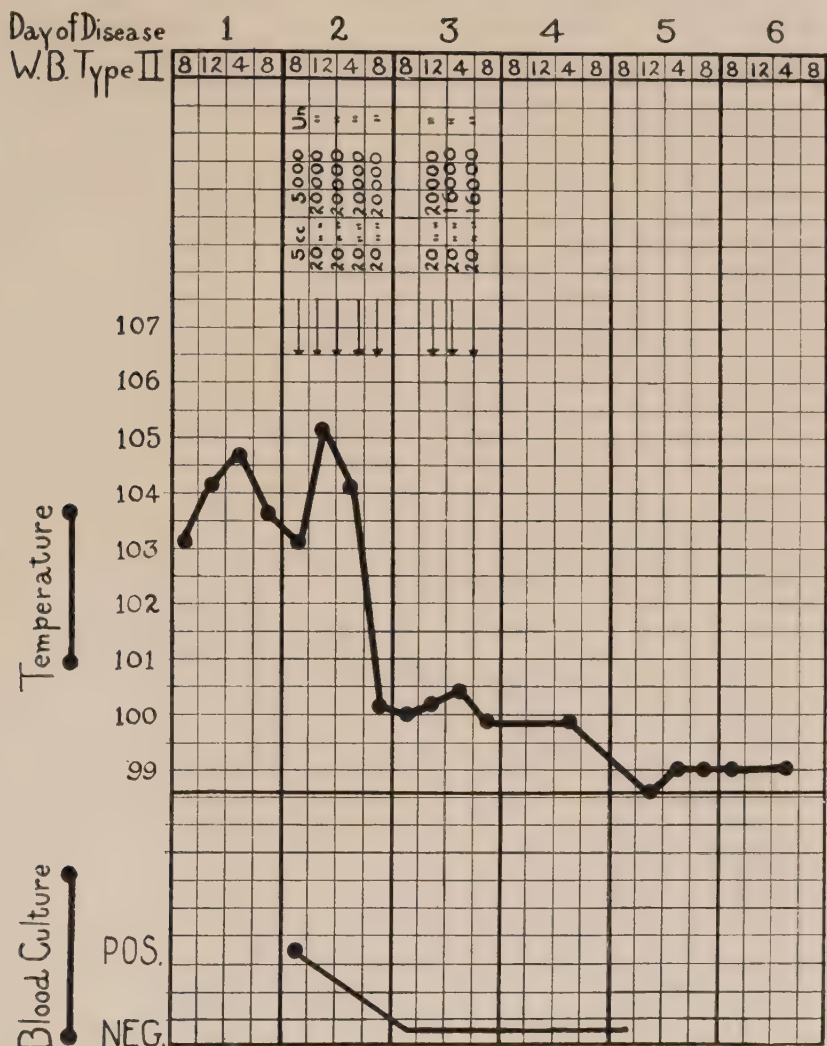
Fig. 7.—Pneumococcus Type II Pneumonia, Admitted to Hospital on First Day of Disease and Treated with Concentrated Antipneumococcus Serum 24 Hours Later.

Blood culture positive. No further observations made on blood culture or protective bodies, but prompt change in general condition and fall in temperature were striking.

systemic disease, chronic alcoholism and age. Moreover, the irregularities all tended in the same direction, that is, toward the production of a high mortality in the untreated group of cases.

The effect of concentrated serum on the death rate in lobar pneumonia is indicated in Table V, which is a summary of the 885 cases of lobar pneumonia included in the study at Bellevue Hospital. Altogether 441 lobar pneumonias fell in the serum-treated group.

TABLE V—DEATH RATE IN CASES TREATED WITH FELTON'S REFINED ANTIPNEUMOCOCCUS SERUM COMPARED WITH DEATH RATE IN UNTREATED CASES

Type	Treated			Untreated		
	Cases	Deaths	Death Rate Per Cent	Cases	Deaths	Death Rate Per Cent
I	153	32	20.9	147	48	32.6
II	106	44	41.5	108	59	54.6
III	40	16	40.0	56	16	28.6
IV	142	40	28.2	133	51	38.3
	441	132	30.0	444	174	39.2

As was to be expected, the most striking results were obtained in the pneumococcus Type I series. In 153 treated cases the death rate was 20.9 per cent, while the control series of 147 cases showed a mortality of 32.6 per cent. Among the pneumococcus Type II cases the results were not quite so striking, but even here there was a decided difference in the mortality for treated and untreated cases—41.5 per cent for the treated series as compared to 54.6 for the untreated cases. In the pneumococcus Type III cases, serum had no beneficial effect. Indeed, the death rate was actually higher for the treated group (40 per cent for the treated, 28.6 per cent for the untreated). This apparent anomaly in the Type III mortality rates is probably due, as noted above, to the presence of an unusually large number of chronically ill patients in the Type III treated series. In the miscellaneous Type IV cases, serum appears to have had a beneficial effect. In a large group of treated cases the death rate was 28.2 per cent as compared with 38.3 per cent for the untreated cases. This may also be due, as shown above, to factors other than serum, which modify the death rate of lobar pneumonia. The death rate for the entire group of 441 treated cases was 30 per cent, while 444 untreated cases showed a mortality of 39.2 per cent.

The pneumococcus complications, such as empyema, meningitis, endocarditis, pericarditis, arthritis and otitis, occurred about as frequently in the treated as in the untreated series. Apparently the serum treatment of pneumonia has very little effect in reducing the incidence of complications.

Refined and concentrated serum appears to fulfill the requisites of an efficient specific agent. It saves monkeys that have been infected with a

lethal pneumococcus pneumonia and septicemia. It usually produces a definite, sometimes a striking clinical effect, on patients with Type I pneumonia when they are treated during the first three days of the disease, and on patients with Type II pneumonia when they are treated during the first two days of the disease. In a large group of treated patients checked by alternate untreated controls, concentrated serum has reduced the death rate one-third in Type I and one-fourth in Type II cases. In the miscellaneous Type IV, the death rate in treated cases appears to have been reduced one-fifth, but this difference might possibly be explained by some other factor, such as the unequal distribution of systemic disease, chronic alcoholism and old age. In the small Type III series, analysis of the figures reveals that a large number of the treated cases was complicated by systemic diseases. This makes it impossible to compare the two groups, and they are included in Table V only for the sake of completeness.

In addition to the experiment conducted at Bellevue Hospital, similar tests with concentrated serum have been carried out at the Harlem Hospital, at the New York Hospital and at the Boston City Hospital. The preliminary report of the results at Harlem Hospital have already been published by Bullowa. His preliminary report on Felton's serum was not particularly promising for the whole group of patients treated. With patients who were treated early, however, the results with serum, particularly Type I, Type II and Type IV cases, were distinctly encouraging.

It is fortunate that Felton has been able to produce a refined derivative of antipneumococcus serum, which can be injected intravenously in adequate amounts without producing thermal reactions. As a matter of fact, a few of the lots which have been used at Bellevue Hospital were found to be chill-producing and their use was discontinued immediately. Though some inequality still exists in the potency of various lots of concentrated serum, this is a difficulty that can be overcome by regulating the dosage in cubic centimeters to meet the potency of the serum in units. The impression was gained that the best clinical results were obtained when doses of 50,000 to 100,000 units per day or more were given early in the course of the disease.

The question of dosage has been studied from the experimental standpoint by Park and Cooper. They recommend the establishment of a "balance of protection," to be measured by the mouse protection test and performed with the patient's blood-serum. They recommend on the basis of their experiments that in the average case an effort should be made to administer 10,000 units in 5 or 10 c.c. of concentrated serum three times a day.

Our own experience in Bellevue Hospital has inclined us to the belief that in general relatively large doses of serum have yielded better results than small doses. It appears from a survey of treated cases in the present series that the best results have been associated with maximum doses of

serum. This is especially true in the production of sharp crises and strik-
ing clinical effects. These have resulted with regularity only when our
program was meticulously carried out and the highest number of units
given. It must be admitted, however, that treatment with large doses is
expensive and for this reason may prove economically impractical.

What are the indications for the serum treatment of pneumonia?
Provided that a concentrated polyvalent antiserum such as that described
above is available, serum treatment would appear to be indicated in
practically all cases of Type I and Type II pneumonia. Whether serum
treatment should be instituted before the pneumococcus type has been
determined is a debatable question. In order to save valuable time, how-
ever, our own inclination would be to administer polyvalent serum
promptly in patients with frank lobar pneumonia as soon as the clinical
diagnosis has been made. If the sputum shows Type I or Type II pneumo-
coccus, serum treatment should be continued. If the case proves to be a
Type III or one of the miscellaneous Type IV infections, serum treat-
ment should be discontinued. In both hospital and private practice the
question will arise whether serum treatment should be administered late
in the disease. Although clinical and experimental evidence would indicate
that in lobar pneumonia, as in other acute infections, serum treatment is
most effective when begun early, there is evidence from the present study
that serum treatment is not without value in some late cases of Type I
and Type II pneumonia.

What are the contra-indications to serum treatment in pneumonia?
At the present time there is no evidence to support the use of serum in
Type III or Type IV pneumonia. In asthmatic cases or in cases who have
previously received large amounts of horse serum, it is questionable
whether serum treatment should be employed at all. In patients who give
a positive skin reaction, serum should be administered with great caution.
Only a small percentage of such patients, however, will give an allergic
reaction after the injection of serum. A positive ophthalmic reaction to
diluted horse serum is a definite contra-indication to serum therapy. It is
also doubtful whether serum should be administered intravenously to
patients suffering with cardiac decompensation, although the writer has
treated several such patients without untoward effects.

Recently we have been working with another refined antipneumococcus
serum prepared by Banzhaf of the New York City Board of Health
Laboratories as follows:

Serum or plasma is saturated with sodium chlorid and the resultant
precipitate is filtered off. To the filtrate is added one-half volume of satu-
rated ammonium sulphate solution to precipitate the pseudoglobulins and
antibodies. This precipitate is filtered off and dialyzed free from salts.

The dialyzed product is added to distilled water and the whole adjusted

to P^{H} 5.6 to precipitate the antibodies. The antibodies are then redissolved in 1 per cent sodium chlorid and the solution passed through a Berkefeld filter.

Felton's serum and Banzhaf's, though prepared by different clinical methods, are practically identical as regards their physical and immunological properties.

At the time of this writing (October, 1928) concentrated antipneumococcus serum is not on the market, but several manufacturers of biological products are now undertaking its preparation, so that within the next few months it should be available to practitioners everywhere.

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CHAPTER XVI

THE THERAPEUTIC USE OF OXYGEN IN PNEUMONIA

Alvan L. Barach

GENERAL CONSIDERATIONS

Historical.—The therapeutic use of oxygen began in the year 1917 when two distinguished physiologists, Haldane and Meltzer, observed that favorable results followed its effective administration. The history of the employment of oxygen prior to this time may be disregarded since it was given haphazardly or in insufficient concentrations. Haldane devised a face mask which was successfully used in cases of pulmonary edema due to war-gas poisoning. Meltzer treated patients with pneumonia with an oral insufflation apparatus and reported marked improvement in some cases. As a result of the beneficial effects of adequate oxygen therapy reported by these two physiologists, an impetus was given to the use of oxygen in clinical disease. During the next ten years the physiologic principles of oxygen-want were reviewed and effective methods of administering oxygen brought to the clinic for the first time.

The physiologic basis for the therapeutic use of oxygen rests on three sets of evidence:

1. The harmful effects of acute oxygen-want were demonstrated by the symptoms of mountain sickness and by laboratory experiments in closed chambers in which the air was artificially deprived of oxygen. Among these effects were cyanosis, rapid pulse rate, disturbances in breathing, nausea and vomiting, slight fever, fatigue, delirium, and finally collapse (Barcroft, Haldane and others).

2. By means of the arterial puncture (Hurter and Stadie) and accurate methods of blood-gas analysis (van Slyke and Haldane), it was shown that the arterial blood of patients with pneumonia at times contained a markedly diminished oxygen content. The degree of arterial oxygen unsaturation found in pneumonia was frequently as severe as that which experimentally induced the symptoms noted above.

3. The administration of 40 to 60 per cent oxygen to pneumonia patients suffering from acute anoxemia raised the oxygen saturation of the arterial blood to or near the normal value (Meakins, Stadie, Barach, and Binger).

Methods.—This evidence threw into sharp outline the problem of devising suitable methods of administering high concentrations of oxygen. Haldane's mask and the oral insufflation method of Meltzer were apt to be so disturbing as to interfere with continuous use. The same criticism may be applied to the mouthpiece and nosepiece rebreathing apparatus of Barach. Oxygen chambers were constructed by Haldane and Barcroft in England,[1] by Boothby at the Mayo Clinic, in Rochester, Minn., by Stadie and Binger at the Rockefeller Institute, and by Barach at the Presbyterian Hospital in New York. They consist of leak-tight rooms which the patient may comfortably occupy in a high concentration of oxygen. They are ventilated by means of motors and pumps which drive the air out of the chamber. This air is then deprived of carbon dioxid, cooled and dried and returned with an additional quantity of oxygen from a tank. An exception to this system is the chamber of Barach, which is ventilated by an internal thermal circulation of the air, a description of which follows.

The first oxygen tent was made by Leonard Hill and consisted simply of a rubberized fabric arranged about the patient in bed. Subsequently, Roth constructed a head tent and Barach and Binger a bed tent. Later, Barach developed a tent in which the air was dried and cooled by direct passage over ice. It consists of a square hood enclosing the head and chest of the patient, and has two windows in front and a window in the top. The ventilation of the latter tent provides a more comfortable atmosphere for the patient, and its use will be described below. The tent, like the chamber, provides an atmosphere rich in oxygen and is ventilated by a closed system which removes carbon dioxid, cools and dries the air which is then rebreathed. A variable proportion of fresh air is drawn into the tent by means of leakage about the rubberized fabric. It has the advantages of a small portable oxygen chamber, and may be used both in the hospital and in the home. Oxygen therapy may be accomplished with precise regulation of the oxygen concentration desired, and with adequate removal of carbon dioxid, moisture and heat. Its disadvantages are that it may become disturbing to the patient because of the noise of the fan which as yet has not been eliminated, and also because of the feeling of enclosure of which some individuals complain. These latter objections can generally be handled by adept psychological management on the part of doctor and nurse. On the whole, this oxygen tent used by the author in over 100 cases in two years has been found very satisfactory. For the physician especially interested in the treatment of pneumonia, it is feasible to learn its use in a short preliminary training. Since it employs a closed system of ventilation, it must be under intelligent supervision. Inasmuch as it is now used in many of the medical and surgical clinics, it is possible for the physician interested in this therapy to become familiar and experienced with it.

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[1] Treatment of patients in oxygen chambers in England was also carried on by Shufflebotham and Sowry and by Campbell, Hunt and Poulton.

The accompanying illustration shows the tent suspended from an arm, carried by a standard which is mounted on an easily movable four-wheeled base. The ventilation is achieved by a light fan and a universal motor. When the tent is to be put into operation, soda-lime is placed in a metal container, 45 pounds generally lasting four days of continuous therapy. Ice, cracked to the size of a man's fist, is put into a second container. The tent-piece is lifted over the patient, the rubberized material folded under
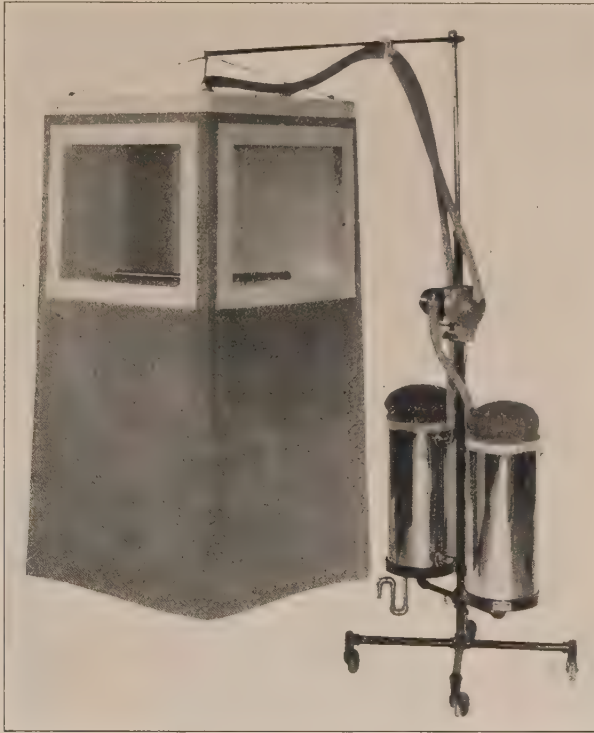
Fig. 1.—Oxygen Tent.
(Courtesy of Warren E. Collins, Mfg.)

the pillow behind and at the side, and the front part is drawn under the sheet across the patient's abdomen. The motor is turned on. The air is drawn from one side of the hood at the top, to the fan, thence passed through the soda-lime and ice containers. It then enters the hood where it is distributed by two perforated aluminum tubes which are adjustable so that the air can be directed toward or away from the patient's face, as desirable. Oxygen is admitted from a high-pressure tank by a calibrated gauge at the rate of 10 liters a minute for ten minutes, and then turned down to 4 or 5 liters, depending upon the leakage in the individual case. The ice is replaced every two hours. Food and medicine are given the patient by the nurse, who puts her hand under the curtain without remov-

ing the tent. The ample window space generally does away with a feeling of enclosure. The oxygen and carbon dioxid tests are simple, and should be performed three times a day, preferably once at night. The concentration of oxygen desired is generally between 40 and 60 per cent, and will be discussed in a consideration of oxygen dosage below.

There is one other method which has stood the test of trial and which is more available for general use than the above, namely, the nasal catheter.
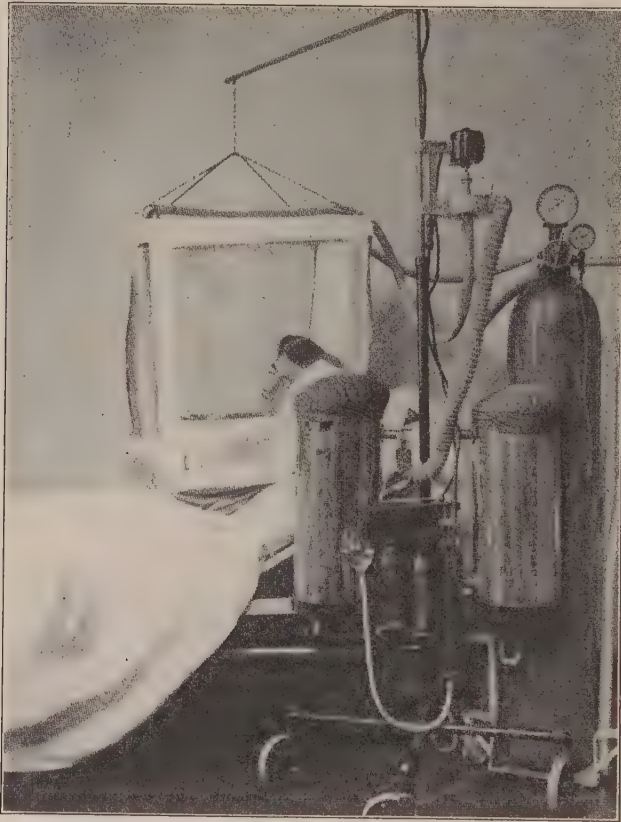
FIG. 2.—OXYGEN TENT IN USE.
(Courtesy of *J. Am. M. Ass.*, Chicago.)

It became known during the war, and when employed under ideal conditions is moderately effective.

The conception of dosage in oxygen therapy is an important one. An investigation of the efficacy of various methods revealed the fact that with the tube and funnel method the oxygen concentration of the inspired air of 21 per cent was increased to 22 to 24 per cent, whereas by means of the nasal catheter it could be increased to 30 to 33 per cent, and in some instances to 35 per cent. An oxygen concentration of less than 30 per cent

rarely has any value, but 30 to 35 per cent oxygen generally lessens cyanosis and increases the arterial oxygen saturation. For the severe cases, an oxygen concentration of 40 or 50 per cent, and occasionally for short periods, 60 per cent may be needed for the maximal beneficial effect of oxygen treatment. Since oxygen tents and oxygen chambers are not universally available, advantage should be taken of a method which has a moderate effectiveness if properly employed. Its use will, therefore, be described in detail.

The nasal catheter should be a No. 10 French (smallest size), perforated one inch from its terminal by four small holes, in order that the stream of oxygen may not lodge continuously on the same part of the mucous membrane. It is inserted as far as the nasopharynx, withdrawn one-half inch so as not to cause gagging, and fastened to the side of the cheek or forehead by adhesive tape. Oxygen is bubbled from a tank at the rate of 2 to 3 liters per minute. In order to accomplish this continuously and without excessive cost, high pressure oxygen and calibrated reducing valves are almost necessary.

FIG. 3.—CALIBRATED REDUCING VALVE.

High-pressure (commercial) oxygen has no disadvantages over so-called medical oxygen; it is enormously cheaper and capable by the use of especially calibrated reducing valves of exact measurement over long periods of time.[2] If 2 liters of oxygen are continuously administered from a 220 cubic foot tank, the treatment with the nasal catheter is continuously maintained for two full days (fifty hours), the patient receiving between

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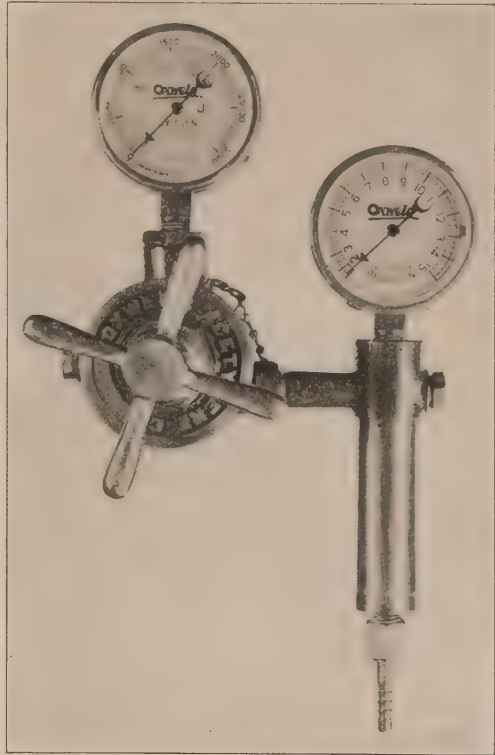
[2] The Oxweld-Acetelene Company, Long Island City, New York, has developed a valve at the request of the author, which is ideally suited for use in connection with the nasal catheter, as well as the tent and chamber. It is calibrated from 1 to 10 liters per minute, has a safety blow-out valve at 100 pounds pressure, and has a silencer when large rates of flow are used. These valves are supplied with directions and personal instruction is given on request.

30 and 35 per cent oxygen in the inspired air. The cost is approximately four dollars. To accomplish this with oxygen from low pressure tanks would involve many changes of tanks, constant adjustment of a low pressure gauge, and very much greater expense.

We have discussed three methods of oxygen therapy in use at the Presbyterian Hospital, New York, for the treatment of oxygen-want in pneumonia. The nasal catheter is the routine method, which we have stated is the ideal method for general use if employed under the conditions specified above. The oxygen tent is a more highly specialized method requiring an additional, although short, training on the part of the doctor. The other more portable forms of apparatus have the disadvantage of inter-
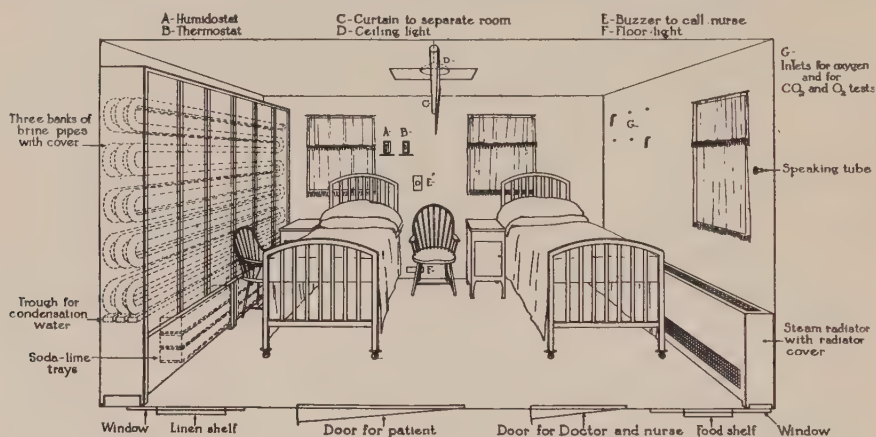
FIG. 4.—OXYGEN CHAMBER.
(Courtesy of The Modern Hospital Publishing Co., Chicago.)

fering with the comfort of the patient and have been abandoned by the author after a thorough trial. The nosepiece rebreathing apparatus is still occasionally employed and is less disturbing than the mouthpiece or the mask.

The oxygen chamber which we have developed at the Presbyterian Hospital is shown in the illustration. It is ventilated by the use of convection currents initiated by a system of brine pipes on one wall and a steam radiator on the other, both concealed by metal covers painted the color of the room. There are no electricity, pumps, fans or motors. The temperature is regulated by a thermostat, the humidity by a humidostat, both acting on valves controlling the inlet of brine and steam. It is more simply run than the tent. The air circulates at the rate of approximately 35 feet per minute. The soda-lime is placed under the brine pipes, and should be replaced once a week. It is the ideal method for the comfort of the patient, and naturally is designed for hospital use only.

INDICATIONS

The physiologic indication for oxygen treatment is acute oxygen-want. It occurs predominantly in pneumonia, both lobar and bronchopneumonia. The clinical indication for treatment is the first appearance of cyanosis, manifested generally in the nail-beds as a bluish tinge, or in the lips. A dark gray or slate-colored appearance in the nails may indicate severe oxygen-want. In the presence of anemia, oxygen is indicated in pneumonia because the transport of oxygen is crippled to begin with. Cyanosis may be absent because the amount of hemoglobin is insufficient to transmit the blue color. The nasal catheter should be instituted early and persisted in until the cyanosis has cleared. In the severe cases, if an oxygen tent or chamber is available, they are to be preferred for the reasons mentioned above. Generally, oxygen treatment should be continued until the patient has had a crisis or is thought to be out of danger.

VALUE OF OXYGEN TREATMENT

When extensive consolidation of the lungs has taken place and the alveolar space is in large part occupied by purulent exudate, the diffusion of oxygen from the air to the blood has been diminished, with a resultant lack of oxygen in the tissues of the various organs. When this condition is of abrupt onset, it may be termed acute pulmonary insufficiency or acute oxygen-want, due to the failure of the lung to transmit its normal supply of oxygen through the alveolar membrane. The harmful effects of impaired lung function (oxygen-want) on the heart, respiration and central nervous system are thus added to the toxemia of the pneumococcus. The degree of oxygen-want varies in different patients. In the mild or moderate instances of impaired lung function, oxygen therapy removes the distressing symptoms due to oxygen-want. In the severe cases it prolongs life by maintaining lung function until perhaps the immunity mechanism overcomes the toxemia of the disease.

Over 100 cases of pneumonia have been treated by the author by means of the oxygen tent or oxygen chamber. Additional cases have been reported by Stadie, Meakins, Binger and Boothby. An analysis of oxygen treatment on the basis of the combined results of these authors supports the conviction that oxygen therapy in adequate doses is beneficial to many, and perhaps life-saving to a limited number. Recently the author reported a series of eight cases of pneumonia in which removal from an oxygen environment was followed by collapse, indicating in these instances that life was being prolonged by oxygen. A recent case of chronic lobar pneumonia Type III was in an oxygen tent for two months before he could dispense with oxygen; on twelve occasions he was removed from the tent, with the recurrence of such alarming symptoms as to necessitate the con-

tinuance of oxygen treatment. When his lungs finally cleared, he was removed without symptoms.

The most obvious effect of oxygen treatment is the clearing of the cyanosis, or its diminution. Increased comfort of the patient and slowing of the pulse rate are generally produced. In some instances the pulmonary ventilation is decreased either by a gradually reduced rate of respiration or a decreased tidal air. According to Boothby, a lowered temperature frequently follows oxygen treatment in pneumonia. In our experience this has often occurred but we have not been as certain of this as of the pulse rate, that the occurrence was due to the inhalation of oxygen. It has seemed to us that delirium was at times noticeably lessened by oxygen treatment.

No statistical evaluation of oxygen therapy in pneumonia is possible at the present time since the severest cases are generally selected for treatment. We arrive at the conclusion that oxygen therapy is valuable from the modification of the course of the disease in individual cases, when oxygen is instituted and at times when it is withdrawn prematurely. The treatment from the point of view that has been outlined is too recent to permit of any conclusions as to its ultimate value, but from the work of others and that of the author, it appears evident that it deserves to be included in the therapy of pneumonia when the indication for it arises.

CHAPTER XVII

THE SERUM TREATMENT OF MEASLES

Jean V. Cooke

Since the first publication of favorable results by Nicolle and Conseil in 1918, the effect of injection of blood-serum from convalescent measles patients in preventing the development of the disease in those exposed to it, has been studied extensively. In general it may be stated that the results of a number of observers [1] have demonstrated that specific prophylaxis in measles is possible in a high percentage of instances, and prophylactic procedures have become an established routine in many localities. It is evident from the many recorded observations that during convalescence and for some weeks afterward the patient's blood contains specific immune substances in considerable amount; that these antibodies persist for many years, although in much lower titer; and that a temporary passive immunity to the infection can be established in susceptible persons by the transfer of a sufficient amount of these antibodies. Since there is at present no way of estimating or standardizing the antibody content of a convalescent's serum, the methods of prophylaxis in use are purely empirical and based on experience.

The temporary immunization by convalescents' serum of all children exposed to measles is not possible at the present time and apparently is not desirable. Since the susceptibility to the infection is so widespread that few children escape it, a temporary immunity would serve merely to defer the attack. The great menace to life that measles carries for infants and young children, however, is a certain indication for an energetic effort to postpone the disease until later childhood, when it is much less serious. The frequency with which measles causes an activation of a previously latent tuberculosis makes it advisable also to protect all children with known tuberculous infection. In general, then, specific measles prophylaxis is especially indicated only in infants and young children, since the methods now available make it practically impossible to protect children of school age who are subject to repeated and unsuspected exposures during an epidemic. Children in institutions, those who are ill with acute or chronic disease, and especially those with known tuberculous infection, should also be protected by specific therapy whenever possible.

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[1] M. G. Peterman, "Prevention of Measles," *Am. J. Dis. Child.*, Chicago, 1928, 36: 123. This article contains a complete bibliography.

Although modified by several factors, the results have shown that 85 per cent or more of children given convalescents' serum during the first week after exposure have failed to develop the infection. In a large proportion of those in whom measles appeared, the disease was of a mild or abortive type. In those given the serum after the first week of the incubation period, the prevention of the disease has been less constant, although many cases have been of a modified, mild variety. In general it is apparent that the sooner after exposure the serum is given, the greater the likelihood of complete protection, since the percentage of measles infections increases rapidly in those injected later than the fifth day. The modified measles observed in certain children given prophylactic serum late, or in insufficient amount, is characterized by slight or moderate fever which lasts only one or two days, by the mildness or complete absence of upper respiratory symptoms, by the rarity of a complicating bronchopneumonia, and by the changed and transient character of the rash. The latter is frequently of irregular distribution and the individual lesions are dwarfed and atypical. Indeed, the rash often would not be identified as measles without the attendant history.

In certain instances, after the administration of convalescents' serum, the incubation period is considerably prolonged. Instead of appearing as usual fourteen days after exposure, the rash may be delayed from one day to a week later. This is of especial importance in releasing children from quarantine after giving serum prophylactically, since such retarded infections are apparently quite as contagious as the unmodified disease. Usually the cases which appear after such prolonged incubation are of a mild abortive type.

The almost complete absence of complications in the modified type of measles when it occurs after the use of convalescents' serum, is of much importance. Measles in itself is a disease of relatively little danger and the mortality is due almost entirely to the accompanying increased susceptibility of the lungs to secondary infection by pyogenic cocci, especially streptococci. More than 90 per cent of the deaths in measles are due to a secondary bronchopneumonia and about three-fourths of these occur in children under three years of age. Any method by which such complications are lessened is therefore life-saving. In this connection it should be emphasized that precautions directed toward the prevention of pneumonia in children suffering from measles are always indicated. It seems certain that, in the majority of cases, the organisms causing the secondary infection are acquired from a healthy carrier who comes in contact with the patient, and the potential menace of all contacts should be kept constantly in mind. A strict quarantine has probably its greatest value in protecting the patient himself from secondary pulmonary infection.

The duration of the passive immunity to measles from convalescents' serum is temporary and can be relied upon for only a few weeks. Those

who develop the modified disease after serum has been given, however, are probably protected permanently. For this reason, and on account of the relative freedom from complications in these milder infections, it would seem advisable often to administer serum even later than the first few days after exposure, in the effort to lessen the severity of the infection.

During convalescence, the optimum time for collecting the serum for prophylactic use is approximately a week after the temperature has become normal. It is, of course, impossible to determine the measles-antibody titer of serum, and it seems probable that the potency in different individuals varies. For this reason it would be expected that pooled sera from several persons would have a more consistent protective action than that from a single individual. In some of the larger cities, in which measles is endemic, the health authorities have limited amounts of pooled serum available to physicians. The serum, if kept sterile, retains its immunological potency for a number of months. When it is not possible to obtain blood from an individual who is recently convalescent, the serum from persons who have recovered from measles several months or even several years previously may be used. In such instances, the antibody content is much lower than that of more recent convalescents and the serum must be used in considerably larger amounts. Even with larger doses, however, such sera are far less efficient in prophylaxis than sera from recent convalescents. A Wassermann reaction should be performed on serum before its use, unless given to another member of the same family. Under conditions which make separation and preservation of serum difficult, whole blood may be used instead. This may be injected intramuscularly immediately after collection, before clotting takes place, or somewhat more readily when the blood is citrated to prevent coagulation.

The dosage of human immune serum employed is quite arbitrary on account of the lack of any method of determining its potency. It has been found that from 2 to 4 c.c. is usually sufficient to protect infants under three years of age if given during the first four days after exposure. Twice this amount is advised for children during the next two days of the incubation period, and 8 to 10 c.c. if given later. As has been previously mentioned, the best results are obtained when the prophylactic dose is given early after the contact. When blood is given from an adult who had had measles some years previously, 40 to 100 c.c. of whole blood or 20 to 50 c.c. of serum must be used, depending on the age of the child and the length of time after exposure. Injections are usually made intramuscularly.

Because of the fact that smaller doses of serum given to children after exposure are often followed by a mild form of the disease which is not accompanied by complications, and since this type of modified measles apparently confers a permanent immunity, some have advised the use of smaller doses of serum in a deliberate effort to modify the disease instead of preventing it. From one-third to one-half the amounts of serum men-

tioned in the foregoing paragraph are used for this purpose. While such a procedure is theoretically an excellent method of active measles prophylaxis, there is some uncertainty about one's ability to graduate the dose sufficiently accurately to produce the modified disease with any constancy. If too small an amount of serum is given, the infection develops unchanged. For this reason it would not seem desirable to adopt the administration of smaller doses routinely but to reserve this procedure for certain special cases.

Blood from convalescents is collected in a sterile flask with aseptic precautions to prevent its contamination. After coagulation, the clot is separated from the glass and the clear serum drawn off after standing. Any excess of red corpuscles may be removed by centrifugation. If the serum is to be used within a short time, and has been collected carefully, no preservative is necessary. When it is to be kept for some time, however, trikresol (one-tenth volume of a 4 per cent solution) should be added to prevent contamination. The slight cloudiness which results does not interfere with the immunizing property of the serum. Such sera retain their potency for a number of months. Whole blood may be drawn into one-tenth its volume of a 5 per cent sterile sodium citrate solution to prevent clotting. Such blood does not keep well and should be used within twenty-four to forty-eight hours after collection. If given intravenously, the usual preliminary tests to assure compatibility are necessary by matching the corpuscles with the recipient's serum, but it may be injected intramuscularly without such precaution.

The value of sera obtained from the immunization of horses or goats by streptococci isolated from measles in prophylaxis is still undetermined. Some immune sera of this type available commercially have proved quite inert. Certain recent reports of a serum prepared from the organism isolated by Ruth Tunnicliff, are quite favorable and suggest a protection similar to that conferred by measles convalescents' serum. Until further experience with such immune serum confirms its value, one must consider that the only effective method in the specific prophylaxis of measles is in the use of convalescents' serum.

The employment of serum for therapeutic use in fully developed measles, even when given during the preëruptive period, has little if any effect on the course of the disease.

CHAPTER XVIII

SCARLET FEVER

Francis G. Blake

INTRODUCTION

The proper utilization of the specific measures now available for the prevention and treatment of scarlet fever demands a clear understanding of the pathogenesis of the disease. It furthermore requires a knowledge of the interrelationships of the three well-recognized phases of the infection, namely, (1) the early toxic phase which is of relatively short duration; (2) the septic phase which may begin with, or at any time after, the onset of the toxic phase and may be more or less indefinitely prolonged; and (3) the sequelæ which, if they occur, commonly appear during the third week, sometimes earlier, sometimes later. To understand the pathogenesis of scarlet fever and the relationships of the three phases of the disease, one to another, it is necessary to have not only a knowledge of the bacterial incitant and the methods by which it attacks the host, but also a knowledge of the means by which the host resists the infection or, if infected, brings about a natural termination of the disease and develops a relatively permanent immunity. It has seemed desirable, therefore, before describing the specific methods of prevention and treatment, to present a brief discussion of these subjects so far as present knowledge permits.

BACTERIAL INCITANT

The studies of Dick and Dick and Dochez, already confirmed by many other investigators, have finally established the long suspected fact that *Streptococcus hæmolyticus* is the bacterial incitant of scarlet fever. The evidence in support of this view may be summarized briefly: *Streptococcus hæmolyticus* is regularly found at the site of the local lesion in scarlet fever; scarlet fever has been experimentally produced in man by inoculation with pure cultures of scarlatinal streptococci under conditions sufficiently rigid to exclude chance infection or the presence of an unrecognized filtrable virus; bacteria-free filtrates of scarlatinal streptococcus cultures contain a soluble substance which in proper dosage causes a local skin reaction in persons susceptible to scarlet fever, no reaction in those who are immune, and if given subcutaneously in sufficient dosage, may cause a general

reaction with an exanthem indistinguishable from that of scarlet fever; serial injections of the culture filtrate induce an active immunity to scarlet fever; serum from animals actively immunized with scarlatinal streptococci or with culture filtrates specifically blanches the rash, neutralizes the toxin present in the blood of patients and cures the essential or toxic phase of the disease; conversely, convalescent scarlet fever serum neutralizes the toxic action of scarlatinal streptococcus culture filtrates.

Whether or not there exist a limited and relatively fixed number of specific biological types of *Streptococcus hæmolyticus,* qualitatively distinguishable by immunological methods from other hemolytic streptococci, which may properly be designated *Streptococcus scarlatinæ,* still remains somewhat uncertain because of much conflicting evidence, and must be left for further investigation to determine. Despite this uncertainty concerning immunological specificity, it nevertheless seems well established that scarlatinal streptococci are possessed of certain pathogenic properties which serve to characterize them. These properties would appear to be at least three in number. The first and most important, which seems to be particularly characteristic of scarlatinal streptococci, is a highly developed toxigenic capacity as compared with that of most other hemolytic streptococci. The second is the invasive and pyogenic property which is apparently common to all pathogenic hemolytic streptococci. The third is the capacity to induce the type of injury represented clinically by the late sequelæ of scarlet fever. This property, which is apparently possessed by many other hemolytic streptococci, will be called the sequelagenic property.

Toxigenic Property.—That scarlatinal streptococci possess a toxigenic property was suggested in 1893 by Bergé, who thought that scarlet fever was due to a local infection in the throat and that the general symptoms were due, as in diphtheria, to the absorption into the circulation of a soluble toxin formed by the streptococcus at the site of the local infection. Observations in support of this opinion were made by Gabritschewsky, in 1907. He found that highly susceptible children inoculated with a vaccine of scarlatinal streptococci developed a general reaction with a rash indistinguishable from that of scarlet fever. He interpreted this as being due to a toxin in view of the negative blood-cultures found in rapidly fatal toxic cases of the disease. Further evidence was provided by Mair, in 1923, in his studies on the Schultz-Charlton rash extinction test, in which he interpreted the blanching phenomenon as being due to the local neutralization of toxin by an antitoxin in the serum. Dochez also held the same opinion in view of the fact that guinea-pigs in which he had established a local focus of infection with a scarlatinal streptococcus occasionally died acutely, apparently from a toxemia, since streptococci could not be cultivated from the blood or body cavities. Finally, Dick and Dick, in 1924, demonstrated a highly potent, soluble toxic substance in bacteria-free culture filtrates of scarlatinal streptococci. Later in 1924, Trask and Blake demonstrated

that a similar soluble toxic substance is present in the blood of patients in the exanthematous stage of scarlet fever. Since 1924 numerous investigations of the toxigenic activity of scarlatinal streptococci have appeared in the literature. In general, these have shown, with some exceptions, that the great majority of scarlatinal strains have the capacity for toxin production highly developed, 0.0001 c.c. or less of the culture filtrate containing sufficient toxin to give a positive skin reaction in susceptible persons, while the majority, though by no means all, of non-scarlatinal strains are relatively poor toxin producers.

Many points of interest concerning the nature, specificity, and mode of action of the soluble toxic substance produced by scarlatinal streptococci still remain uncertain. While it appears to resemble diphtheria toxin, for example, in that it is a soluble product given off into the surrounding medium during the growth of the streptococcus in culture or in the tissues of the host, and is antigenic in that it stimulates the production of a neutralizing antitoxin, it differs from it in that it is relatively heat stable, in the rapidity with which it apparently induces antitoxic immunity, and in its lack of significant toxicity for many normal animals and for very young infants, even though the animals and newborn infants possess no demonstrable antitoxin in the blood. In fact, there is an increasing body of evidence which makes it seem probable that it is not a true primary exotoxin, and that susceptibility to its toxic action is an acquired sensitiveness in the nature of an allergic phenomenon.

In spite of the uncertainties mentioned above, it nevertheless appears well established that the soluble substance elaborated by the scarlatinal streptococcus, which for convenience of terminology has been called a toxin,[1] causes in sensitive persons the essential toxic phenomena of scarlet fever which establish the disease as a clinical entity. These phenomena are the exanthem, the enanthem, the strawberry tongue, the general toxic symptoms of the exanthematous stage (fever, rapid pulse, vomiting, and psychic disturbances) and probably the urobilinuria and the jaundice, when it occurs. The important evidence for this may be briefly stated: Subcutaneous injection of the toxin in sensitive persons has been shown by Dick and Dick and others to cause a general toxic reaction accompanied by a typical scarlatinal rash; Blake and Trask have shown that the toxin is present in the blood during the early toxic and exanthematous stage of the disease and disappears from the blood with the fading of the rash, even though the septic phase of the disease continues; numerous observations have shown that neutralization of the circulating toxin by antitoxin treatment causes a prompt disappearance of the rash and general toxic symptoms, even though the symptoms attributable to a coexisting septic process may not disappear.

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[1] Toxallergen is probably a more suitable term for this substance.

Invasive and Pyogenic Properties.—The invasive and pyogenic properties of the scarlatinal streptococcus are evident from the wide variety of focal and generalized septic processes such as sinusitis, otitis media, mastoiditis, meningitis, adenitis, and pyemia, often caused by this organism in patients with scarlet fever. Whether or not these properties of scarlatinal streptococci differ in degree from those of other hemolytic streptococci is uncertain so far as the human host is concerned. While such little animal experimentation as has been done would seem to indicate that most scarlatinal strains are relatively avirulent for the usual laboratory animals, it is well recognized that results obtained in these animals may not correspond with what occurs in the human host. Of greater importance is the probable fact that the invasive and pyogenic activities of the scarlatinal streptococcus are not directly dependent upon the toxigenic property of the organism. This is clearly suggested, first, by the fairly frequent occurrence of the so-called *scarlatina sine exanthemate,* long recognized as a clinical entity and recently established through the studies of Stevens and Dochez, Nicholls and others as a pyogenic infection with *Streptococcus scarlatinæ* in persons with an antitoxic immunity and consequently not susceptible to true clinical scarlet fever; secondly, by the observations of Blake and Trask on the relation between the toxic and septic phases of scarlet fever, in which they have found that the pyogenic lesions may progress after the specific toxemia has disappeared and even in the presence of an excess of antitoxin in the circulation. Although the invasiveness of scarlatinal streptococci does not appear to be dependent upon their specific toxigenic capacity, it nevertheless seems probable that the initial development and early progress of pyogenic lesions in scarlet fever is favored by the toxic injury to the patient. While this is, at present, an assumption unsupported by experimental evidence, it would appear to be suggested at least by the well-recognized clinical fact that septic complications are much more frequent in scarlet fever than in ordinary hemolytic streptococcus tonsillitis, for example, and supported by the fact that early neutralization of the specific toxemia of scarlet fever by antitoxin treatment often appears to exert a favorable influence on existing pyogenic complications and to prevent to a considerable extent their subsequent development.

Sequelagenic Property.—The third pathogenic property of scarlatinal streptococci is that property which is responsible for the late sequelæ of scarlet fever, notably acute glomerulonephritis, non-suppurative adenitis, and non-suppurative arthritis. Although theories have been suggested, little if anything is actually known at present concerning the nature of the process underlying the development of these sequelæ. The fact that they occur a week or more after the toxic stage of the disease has terminated, that their occurrence appears to be independent of the severity of the toxic phase, and that they may develop, even though antitoxin is present in the blood, suggests that they are not directly due to the specific toxin. This is

further supported by the fact that similar sequelæ are not infrequent following non-scarlatinal streptococcus infections. Schick, as long ago as 1907, suggested that the sequelæ might be allergic in nature, because they occur at a time when hypersensitiveness might be expected to develop, because the arthritis and adenitis are clinically comparable to the arthritis and adenitis of serum disease, and because an increase in eosinophilic leukocytes is common in this stage of scarlet fever. If so, it seems more probable that the sequelæ represent an allergic type of reaction to unknown products, presumably protein in nature, liberated during growth or dissolution of the streptococci in the body, than to the specific toxin. Only further investigation can elucidate this problem and remove it from the realm of hypothesis.

SUSCEPTIBILITY AND IMMUNITY

Knowledge concerning the factors which determine the susceptibility of the host to the various pathogenic activities of the bacterial incitant and of the immunity processes by means of which the host combats these activities is as important for the understanding of the pathogenesis of scarlet fever as knowledge of the pathogenic properties of *Streptococcus scarlatinæ*.

Susceptibility to the Toxin.—Since it seems clearly established that the soluble toxin or toxallergen produced by scarlatinal streptococci is responsible for the characteristic clinical phenomena of the disease, susceptibility to scarlet fever should depend, in part at least, upon susceptibility to the action of the toxin. That this is so seems now to be thoroughly proven by the results obtained with the Dick test. This test consists in the intracutaneous injection on the flexor surface of the forearm of 0.1 c.c. of a standardized dilution of scarlatinal toxin obtained from sterile filtrates of scarlatinal streptococcus cultures. The test is read twenty to twenty-four hours after the injection. It is considered positive when a local erythema 1 centimeter or more in any diameter results, negative when there is either no reaction or one less than 1 centimeter in diameter. A positive test indicates susceptibility to the toxin or in other words the lack of an effective antitoxic immunity. A negative test indicates insusceptibility to the toxin, *i.e.,* with one important exception to be mentioned below, the presence of an effective antitoxic immunity. In support of this view it has been shown by the studies of Henry and Lewis, Davies, Debré and others, that, with rare exceptions, persons giving a negative Dick test contain a measurable amount of scarlatinal antitoxin in the blood, while those giving a positive test possess little or no antitoxin, and that there is an inverse relation between the skin reactivity of the individual and the amount of antitoxin in his blood. The one important exception is in the case of newborn and very young infants, nearly all of whom, as first shown by Cooke, give a negative skin test even to multiple skin test doses of toxin, irrespective of

whether their mothers are Dick-positive or Dick-negative and irrespective of whether they have a passively transmitted antitoxic immunity or not. This fact indicates that in many infants a negative test shows a lack of susceptibility to the toxin rather than the presence of antitoxic immunity, and suggests the probability that susceptibility to the toxin, which ordinarily does not reach its highest point until some time during the second year of life, is an acquired susceptibility or allergy.

While it is undoubtedly true that the Dick test, except in very young infants, is a remarkably reliable measure of the presence or absence of antitoxic immunity and consequently is of very great practical value in determining susceptibility or immunity to scarlet fever, it nevertheless should be borne in mind that many persons giving a positive test may be frequently exposed to scarlet fever and still not contract the disease, and that not a few persons giving a negative test may, through exposure to scarlet fever, become infected with *Streptococcus scarlatinæ* and develop tonsillitis or some other focal infection due to this organism without developing clinical scarlet fever. It seems probable, therefore, that a positive test, though indicating susceptibility to the toxin, does not necessarily indicate susceptibility to infection, and quite certain that a negative test, though indicating immunity to the toxin, does not necessarily indicate resistance to infection. It should be emphasized, however, that, even though the Dick test does not appear to be a measure of susceptibility or immunity to infection with *Streptococcus scarlatinæ,* this fact does not impair its value as a practical method for differentiating between those who may be and those who are not susceptible to the clinical entity of scarlet fever.

Susceptibility to Infection.—The nature of susceptibility to the invasive and pyogenic activities of scarlatinal streptococci is in reality but vaguely understood. The mechanism of resistance to infection, though often called antibacterial immunity, is equally obscure. Two facts, however, seem fairly well established. In the first place, immunity to infection would appear to be different from antitoxic immunity and consequently, as suggested above, not measurable by the Dick test. In the second place, antibacterial immunity would appear to be more or less independent of antitoxic immunity and not to parallel it. That resistance to infection may be wanting in persons who possess an effective antitoxic immunity is evidenced (1) by the not infrequent occurrence of pyogenic infections with scarlatinal streptococci in individuals exposed to scarlet fever, who at the same time give negative Dick tests and possess sufficient antitoxin in the blood to prevent their developing scarlet fever, even though severely infected with *Streptococcus scarlatinæ ;* and (2) by the fact that the pyogenic or septic phase of scarlet fever may persist long after the patient has developed an antitoxic immunity, as shown by the termination of the toxic phase of the disease, the disappearance of toxin from the circulating blood and the appearance of a considerable amount of antitoxin in the blood.

Whether or not an antibacterial immunity may be present in the absence of an antitoxic immunity is not known with certainty, since there is, at present, no reliable method for measuring antibacterial immunity, but it seems at least probable that this may be so, since it is a common observation that many Dick-positive persons, though frequently exposed to scarlet fever, nevertheless fail to contract the disease. This apparent lack of identity and parallelism between antibacterial and antitoxic immunity is of great importance to the understanding of the relationship between the septic and the toxic aspects of infection with *Streptococcus scarlatinæ*. It furthermore has an important bearing on prevention, on the indications for antitoxin treatment and on the therapeutic results to be expected from the use of antitoxin.

Susceptibility to Sequelæ.—Concerning the nature of susceptibility or immunity to the sequelæ of scarlet fever little or nothing is known, except that the development of an antitoxic immunity following the recovery from the acute toxic stage of the disease does not preclude the development of sequelæ. The allergy theory of Schick has already been mentioned, but it requires no further comment, since it is largely hypothetical at present.

PATHOGENESIS

On the basis of the foregoing considerations concerning the pathogenic properties of scarlatinal streptococci and the defensive mechanisms of the host against these pathogenic properties, it is possible to construct, even though there are still many gaps in our knowledge, a tentative conception of the pathogenesis of scarlet fever, much of which rests upon sound experimental evidence. From the evidence at present available, it would appear that the occurrence of scarlet fever probably depends primarily upon the infection [2] of a susceptible (to infection) and toxin-sensitive or allergic host possessing little or no antitoxic immunity by a hemolytic streptococcus characterized particularly by a highly developed toxigenic capacity, but also possessing invasive and pyogenic properties against which the host may be highly or little, though never completely, resistant. An effective resistance to infection, even in a Dick-positive or toxin-sensitive host, would obviously preclude the occurrence of scarlet fever just as effectively as a high degree of antitoxic immunity, while lack of resistance to infection in a Dick-negative person might lead to disease (tonsillitis, etc.), but not to true scarlet fever, since the essential toxic phase of the disease would be wanting.

The pathogenesis of the essential phenomena of the disease represented clinically by the early toxic and exanthematous stage may be ascribed to the action of the toxin which is absorbed into the circulation from the local

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[2] The term infection is used in the usual clinical meaning and implies a sufficiently heavy infection to result in clinical evidence of disease.

focus of infection commonly situated in the throat. The pathogenesis of the septic phenomena, which are quite unessential to the disease, though frequently present, may be ascribed to the invasive and pyogenic activities of the bacterial incitant in a host possessing relatively little antibacterial immunity. Depending upon the relative degrees of toxin sensitivity and susceptibility to infection and invasion, one or the other phase of scarlet fever may dominate the picture in the individual case. Concerning the pathogenesis of the sequelæ there is no positive evidence warranting a conclusion.

The interrelationships and duration of the toxic and septic phases of scarlet fever have been studied in some detail by Blake and Trask. They have found that the toxic phase as measured by the presence of toxin in the blood, in the absence of pyogenic lesions other than simple tonsillar infection, is not only self-limited but also of relatively short duration, ordinarily having reached its height by forty-eight to seventy-two hours after onset and rarely, if ever, exceeding a period of six days from the beginning of the disease. With the early development of even relatively mild pyogenic lesions, such as moderate purulent rhinopharyngitis and cervical adenitis, the degree of the toxemia is considerably increased and its duration prolonged so that it does not ordinarily reach its height until the fifth to sixth day of the disease, after which time it diminishes rapidly in severity, even though the pyogenic lesions continue. With the early development of more severe septic lesions, such as severe purulent rhinopharyngitis with or without sinusitis, otitis media with or without mastoiditis, severe cervical adenitis, ulcerative tonsillitis, peritonsillar abscess, etc., the degree of toxemia is still further enhanced and usually increases much more rapidly to a high grade during the first three days of the disease where it is often maintained until the seventh or eighth day. During the second week of the disease, however, even though the septic lesions progress and become more severe, the toxemia rapidly abates. So far as present, somewhat limited observations show, toxin has been found in the blood only in moderate amount after the eighth day and none has been found later than the thirteenth day. The course and severity of the toxemia in non-septic, moderately septic and severely septic cases is shown in Figure 1, which is based on a study of toxin in the blood of 132 cases of scarlet fever. From this it is clear that the toxemia closely parallels the exanthem, increasing as the exanthem develops, diminishing as the exanthem fades. The important effect of early septic lesions on the severity of the toxemia during the first week of the disease is also evident.

PROPHYLAXIS

Three measures are available for the prevention of scarlet fever: (1) Isolation and disinfection, (2) active immunization, (3) passive immunization.

Isolation and Disinfection

Since no significant modifications in the isolation and disinfection measures long employed in preventing the spread of scarlet fever have resulted from the newer knowledge of the etiologic relationship of *Streptococcus hæmolyticus* to the disease, these measures will not be discussed. It should be pointed out, however, that prompt cure of scarlet fever by antitoxin treatment does not appear to hasten the disappearance of scarlatinal streptococci from the throat of the convalescent patient (Nicholls), so that the minimum required period of isolation cannot be shortened, unless it can be demonstrated by repeated culture that hemolytic streptococci are no longer present in the throat. A second point of importance in the field of prophylaxis is the probably much greater prevalence of pyogenic infections with *Streptococcus scarlatinæ* (*scarlatina sine exanthemate*) during periods when scarlet fever is epidemic than had hitherto been supposed. These infections have been shown by Stevens and Dochez to be a source for the spread of scarlet fever and the question may justly be raised whether they should not be as rigidly isolated as cases of true scarlet fever.

Active Immunization

The method of active immunization most widely used at present is that introduced by Dick and Dick in 1924 and consists of a series of subcutaneous inoculations of increasing amounts of standardized scarlatinal toxin. The toxin employed consists of the filtrate of broth cultures of *Streptococcus scarlatinæ,* the unit of toxin being the skin-test dose described by Dick and Dick. While it seems clearly established that 90 to 100 per cent of Dick-positive susceptible individuals can be rendered Dick-negative and immune to scarlet fever by this method, many practical points concerning dosage, the use of monovalent, polyvalent, or modified toxins, duration of immunity, and indications for immunization still remain uncertain. Consequently, as recently pointed out by Kiefer, no standard rules of procedure can be formulated at the present time, which may not be modified by further experience.

Indications for Active Immunization.—The first and most important indication for active immunization is, of course, susceptibility to scarlet fever as determined by the Dick test, since it has been well established that persons showing negative Dick tests, with rare exceptions, already possess sufficient immunity to prevent their contracting scarlet fever. To what extent and under what circumstances active immunization of positive reactors should be advocated is a subject concerning which there is still much difference of opinion. There would appear to be, however, at least two groups of individuals in which immunization should be carried out: (1) nurses and others engaged in the care of scarlet fever patients in

hospitals, (2) institutional groups where scarlet fever is apt to be prevalent. Complete immunization to the point of a negative Dick test will result in practically complete elimination of scarlet fever from these groups (Dick and Dick, Hektoen and Johnson, Toomey). Active immunization should furthermore be carried out in the case of individuals who request it. It has been advocated by Kinloch, Smith and Taylor in the case of Dick-positive members of any family in which a case of scarlet fever has occurred, and should be done before release of the patient from isolation in order to prevent return cases. The general use of active immunization in the public schools is being extensively tried, but must be considered to be in the experimental stage at present, until the most practical method of immunization and the duration of the immunity are more accurately defined.

Method.—As pointed out above it is not possible to state at present what the best method of immunization is. Dick advises the use of five subcutaneous injections of 500, 2000, 8000, 25,000 and 65,000 skin-test doses of toxin given at intervals of five to seven days. While this amount would appear to be necessary to immunize the more highly susceptible, it is undoubtedly more than is required for many moderately susceptible individuals. This is shown by the report of Kiefer who has recorded that of approximately 6000 Dick-positive school children treated with 500, 3000 and 20,000 skin-test doses, 90 to 95 per cent gave a negative reaction on retest. Because of the obvious practical difficulty in completing a series of five injections in many instances, it would appear more advisable to give an initial series of three injections of 500, 2000 and 10,000 skin-test doses, followed after two weeks by a retest, and to continue the injections only in those who still give a positive Dick test.

Numerous modifications of the Dick method of immunization, particularly with respect to the antigen used, are being tried. These include ricinoleated antigen, vaccines, combinations of vaccine and toxin, and polyvalent toxins. These studies are still in the experimental stage. Decision as to their relative merits must await further experience.

Results.—Active immunization, whatever method is employed, *provided it is carried to the point of an entirely negative Dick reaction,* results in immunity to scarlet fever in nearly all instances. The occasional exceptions reported in the literature are too few to invalidate the undoubted value of immunization in preventing scarlet fever. Fortunately, immunity develops rapidly and is ordinarily established within two weeks after the last injection of toxin. As in the case of diphtheria, highly susceptible individuals comprising 5 to 10 per cent of Dick-positive reactors are apparently extremely difficult or almost impossible to immunize rapidly or even completely. This is perhaps due to a complete lack of basal immunity or of the mechanism for developing immunity. The duration of immunity is still somewhat uncertain and apparently varies with the individual and perhaps

with the dosage and number of injections of toxin. Kiefer reports that of 799 Dick-positive children given 500, 1000 to 1500, and 3000 to 4500 skin-test doses, 39 per cent were Dick-negative twenty-one days after the third injection. The remaining 61 per cent were given a fourth injection of 5000 skin-test doses and all but 11 per cent were negative fourteen days later. Of the remaining 11 per cent all but nine cases who were lost trace of were rendered Dick-negative by further injections. Three years later 577 of the original 799 were retested and it was found that 131, or 29.3 per cent, had changed from negative back to positive. In another group of ninety children immunized in 1926 with 500, 3500 and 30,000 skin-test doses, 34 per cent had again become positive when retested in 1928. A third group, eighteen years of age or older, immunized between March, 1926 and January, 1927, with 500, 5000 and 30,000 skin-test doses were retested in May, 1928, and 39 per cent were found to have changed back from negative to positive. From these results it would appear that 60 to 70 per cent of those immunized to the point of a negative Dick reaction maintain their immunity for at least two or three years, while 30 to 40 per cent become susceptible again within one to three years.

General reactions from toxin injections are very infrequent and are transitory. They consist of nausea, vomiting and rash in order of frequency. They are of no more consequence than the occasional reactions occurring with vaccination against typhoid or toxin-antitoxin immunization against diphtheria.

Finally, it should be pointed out that the conversion of Dick-positive susceptible individuals to Dick-negative immune individuals by active immunization with scarlatinal toxin, though resulting in an antitoxic immunity to scarlet fever, does not necessarily result in an antibacterial immunity to infection with *Streptococcus scarlatinæ*. In fact, Kinloch, Smith and Taylor have found an increased number of cases of *scarlatina sine exanthemate* among nurses since the introduction of toxin immunization, though no true scarlet fever has occurred. Hektoen and Johnson, on the other hand, have reported a reduction in the incidence of sore throats following immunization of nurses against scarlet fever.

PASSIVE IMMUNIZATION

Temporary passive immunization against scarlet fever can be accomplished by the intramuscular injection of 3000 units of scarlatinal antitoxin. This method is, in general, inadvisable, because not more than 10 per cent of those exposed to scarlet fever ordinarily contract the disease, because it provides only a transient immunity of three to six weeks, because of the inconvenience of serum disease, and because scarlet fever, if contracted, can be promptly cured by the therapeutic administration of antitoxin. When exposure has occurred Dick tests may be performed to deter-

mine the susceptibles and these should be kept under close observation for a week to ten days and given a therapeutic dose of antitoxin on the appearance of symptoms of scarlet fever. Dick also advocates culturing the throats of exposed individuals for hemolytic streptococci and recommends that susceptibles with negative cultures be actively immunized at once, those with positive cultures be immunized later after the preliminary period of observation.

In exceptional circumstances, when it is important that the possibility of contracting scarlet fever be temporarily eliminated, a prophylactic dose of antitoxin may be given, but the individual or, if a child, the parents should be forwarned of the possibility that serum disease will result.

ANTITOXIN TREATMENT

The specific treatment of scarlet fever with antitoxin was first successfully employed by Moser in 1902 and by Savchenko in 1905. Despite the excellent results obtained by them serum treatment failed to receive acceptance, presumably because the etiologic relationship of *Streptococcus hæmolyticus* to scarlet fever was viewed with skepticism and because no method of standardizing the serum was available, so that inferior products appeared which had little or no curative value. In 1923, Dochez produced a highly potent scarlatinal antitoxin by the immunization of horses with a series of subcutaneous injections of nutrient agar into which a living culture of *Streptococcus scarlatinæ* had been inoculated. This serum was shown by Blake, Trask and Lynch to blanch specifically the rash of scarlet fever patients when injected intracutaneously and to possess a striking curative effect when administered intramuscularly early in the course of the disease. In 1924, Dick and Dick also reported on a scarlatinal antitoxin prepared by the immunization of horses with repeated injections of scarlatinal toxin alone. These antitoxins have now received extensive clinical trial and have proved to be of undoubted value in the treatment of scarlet fever, *provided serum with a high antitoxin content is used in adequate amount early in the disease.*

Preparation and Standardization of Antitoxin.—Scarlet fever antitoxin may be prepared by the immunization of horses by the Dochez method, by the Dick method or by combined immunization with toxin and living cultures of *Streptococcus scarlatinæ*. Which method is the most efficient and economical is at present uncertain, but as pointed out by Wadsworth, Kirkbride and Hendry the end to be attained, whatever method of immunization is employed, is a serum of high potency and polyvalency, since the efficiency of serum therapy primarily depends upon these qualities in the serum used.

The standardization of antitoxin is performed by determining in a series of Dick-positive persons the highest dilution of serum which will

completely neutralize in each person the toxic action of one skin-test dose of standard toxin and comparing the results in the same test subjects with neutralization of the toxin by a standard antitoxin of known strength. According to present regulations of the United States Hygienic Laboratory one unit of antitoxin is that amount which will neutralize 50 skin-test doses of toxin. In the opinion of Wadsworth, with which the writer concurs, it would be better if the unit were that amount which would neutralize 100 skin-test doses, since the lower unit gives a higher numerical value to serum of low potency while the higher favors higher standards of serum production.

It has been shown by Blake and Trask and by Park that the minimum therapeutic dose required in the treatment of mild or moderate cases of scarlet fever is 6000 to 8000 units of antitoxin (United States Hygienic Laboratory standard). In order to meet this requirement and at the same time have a minimum therapeutic dose of 10 c.c. in volume, it is necessary that scarlet fever antitoxin should contain at least 800 United States Hygienic Laboratory units per cubic centimeter. It was found by Blake and Trask in 1925 that many antitoxins then available for the treatment of scarlet fever were far below this potency and also far below the potency indicated by the label. That this unfortunate situation still exists in 1929 is shown by the studies of Wadsworth, Kirkbride and Hendry, who have shown not only that many antitoxins at present available test far below the potency shown on the label but also that they are deficient in polyvalency. Universally satisfactory results in the treatment of scarlet fever with antitoxin cannot be expected until polyvalent serum of high potency is generally available. Wadsworth has found that thus far this result has apparently been best attained by immunization with the streptococcus strain, Dochez, N. Y., no. 5. Until the standards for the production of scarlet fever antitoxin are as high and as rigid as in the case of diphtheria antitoxin much disappointment and skepticism concerning the value of scarlatinal antitoxin is bound to occur.

Indications for Antitoxin Treatment.—It is now well established that the curative action of scarlatinal antitoxin is largely, if not entirely, due to its capacity to neutralize scarlatinal toxin. The evidence in support of this view may be summarized briefly as follows: (1) Intracutaneous injection of antitoxin in patients with scarlet fever produces a local blanching of the rash, thus indicating its ability to neutralize the action of the toxin in the tissues; (2) intramuscular injection in therapeutic dosage is promptly followed by disappearance of toxin from the circulating blood and the appearance of demonstrable antitoxin in the blood, a fact which shows the ability of the antitoxin to neutralize *in vivo* the circulating toxin in those acutely ill with scarlet fever; (3) adequate antitoxin treatment in toxic cases of scarlet fever results in a critical cure of the disease; (4) early adequate treatment in toxic and septic cases promptly cures

the specific toxic aspects of the disease, but appears to benefit the septic aspects only indirectly by neutralizing the specific toxemia; (5) treatment of late severely septic cases often yields disappointing results; (6) in post-scarlatinal sepsis after the toxic stage has terminated, antitoxin exerts no demonstrable therapeutic effect.

Since it has been shown, as described above in the paragraphs on pathogenesis, that the toxic phase of scarlet fever develops promptly after onset and that the toxemia is increased in severity and prolonged by pyogenic or septic complications while the rash is still present, and since it is well recognized that the incidence and relative importance of the septic aspects of scarlet fever steadily increase as the diseases progresses, it is clear that the best results from antitoxin treatment will be obtained only when antitoxin is given early in the disease before the septic phase has become the dominant factor in the illness.

On the basis of the foregoing considerations the indications for treatment may be stated briefly. In all early cases of more than very moderate severity and in all early cases, whether apparently mild or not, in which pyogenic extension of the local infection beyond the tonsils is present or beginning to appear, antitoxin should be given at once as soon as the diagnosis is made. In cases seen for the first time later in the disease, whether septic or not, the continued presence of the exanthem is the best indication for treatment. If the rash is still present antitoxin should be given, if it has disappeared no benefit is to be expected from antitoxin and it should not be used.

Whether or not all mild, uncomplicated cases should be treated is a matter concerning which there is difference of opinion at the present time. Undoubtedly most mild cases recover naturally, but it should be borne in mind that some cases, apparently mild at onset, rapidly and unexpectedly become severe. In case of doubt it would seem wiser to give antitoxin, in view of its demonstrated curative value, than to postpone treatment in the hope that the case will remain a mild one and recover promptly.

Method of Administration.—Antitoxin should be administered intramuscularly or intravenously, never subcutaneously. In the great majority of cases intramuscular injection is satisfactory. The full amount required should be given in one treatment, inasmuch as one adequate dose given early is far more efficacious than the same amount given in divided doses. The anterior or lateral aspect of the mid-thigh is the most satisfactory site for the injection. Only in extremely toxic cases is intravenous injection necessary.

Failure to estimate properly the degree of toxemia at the time of the first treatment may result in the use of an inadequate dose of antitoxin. Under these circumstances a second dose becomes necessary. The important clinical indication that a second treatment is needed is failure

of the rash to fade within twelve to twenty-four hours after the first treatment. In purely toxic cases without pyogenic or septic complications the temperature and pulse rate should fall if the first dose has been adequate; in septic cases the temperature may remain more or less elevated due to the pyogenic complications, even though the toxin has been neutralized and an adequate excess of antitoxin has been established in the patient's blood. In late cases, or those with a hemorrhagic rash it is necessary to distinguish between the erythema and the pigmentation of the skin in determining whether the exanthem has faded in response to treatment, failure of the erythema to fade being the real indication of inadequate treatment, existing pigmentation and hemorrhage naturally not being affected by antitoxin.

As in the administration of any antiserum, it is a wise precaution before giving antitoxin to test the patient for hypersensitiveness to horse serum by means of an intracutaneous injection of 0.05 c.c. of a 1:10 saline dilution of serum. Hypersensitiveness will be indicated by a local wheal and erythema reaction developing within five to fifteen minutes. This is particularly important when the patient is subject to asthma, hayfever or urticaria, or when intravenous treatment is contemplated. If the patient is hypersensitive, he should be desensitized by the usual method of giving fractional dosages of antitoxin at twenty-minute intervals. Adrenalin should always be ready for immediate injection and be given at once, 0.5 to 1 c.c. intramuscularly or intravenously, should anaphylactic symptoms appear. It may be repeated as often as necessary to control the symptoms.

Dosage.—The end to be attained in the treatment of scarlet fever with antitoxin is the prompt neutralization of toxin in the blood and tissues and the simultaneous establishment of a considerable excess of antitoxin in the circulating blood of the patient in order that additional toxin elaborated at the site of the local lesion may be neutralized before it reaches other parts of the body. The number of units of antitoxin required to accomplish this result will vary with the size of the patient and particularly with the severity of the toxemia, which in turn varies within wide limits in different patients. By measuring the number of units of toxin in the blood of twenty-five patients with scarlet fever of varying grades of severity Trask found values ranging from 1/4 skin-test dose to 330 skin-test doses per c.c. of patient's serum.

Although accurate estimation of the severity of the toxemia in the individual case ultimately depends upon clinical experience and judgment, much assistance may be obtained from the study by Blake and Trask on the relation of the course of the disease to the degree and duration of the toxemia portrayed schematically in Figure 1. It will be seen at once from this figure that the most important factors influencing the degree of the toxemia are the duration of the disease and

especially the presence and severity of pyogenic or septic complications *during the exanthematous stage.*

In simple toxic cases (Fig. 1*a*) with no extension of the local infection beyond the initial focus, which is commonly in the tonsils, the degree of toxemia is mild in approximately 40 per cent of cases, moderate in 40 to 50 per cent and severe in 10 to 20 per cent. Differentiation of these grades of severity within the group depends upon clinical observation of the severity of the general symptoms and the intensity and
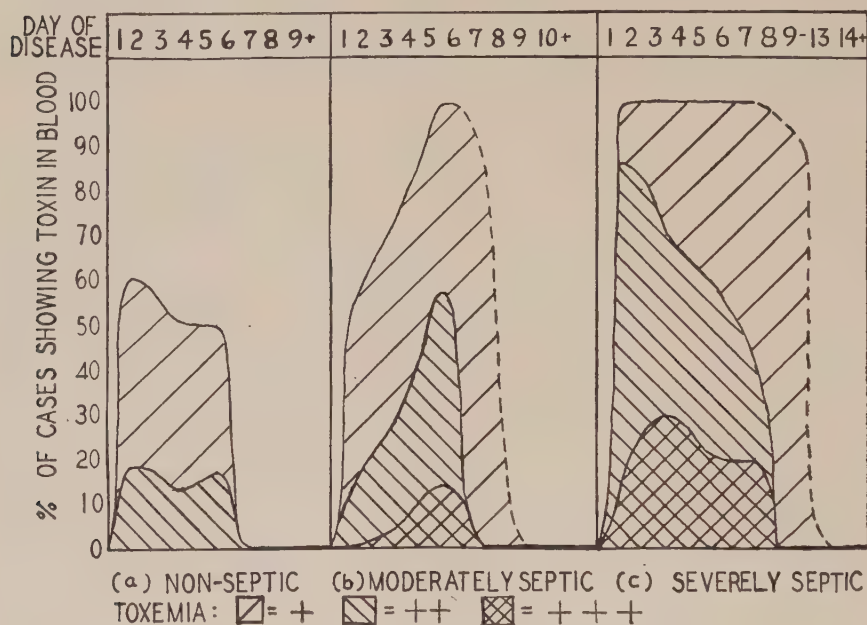
FIG. 1.—DURATION AND DEGREE OF TOXEMIA IN (*a*) NON-SEPTIC, (*b*) MODERATELY SEPTIC, AND (*c*) SEVERELY SEPTIC SCARLET FEVER.

extent of the rash. Six thousand to twelve thousand units of antitoxin is ordinarily an adequate dose.

In patients with extension of the initial focus of infection and the development of only moderately severe pyogenic lesions (Fig. 1*b*), such as moderate purulent rhinopharyngitis or cervical adenitis, the degree of toxemia is essentially the same as in the simple toxic group during the first forty-eight hours of the disease, but after this period the toxemia increases rapidly, approximately 40 per cent developing severe toxemia and 15 per cent extreme toxemia between the third and sixth days of the disease. After this period the toxemia ordinarily abates rapidly with the fading of the exanthem. In order to provide with certainty an adequate excess of antitoxin this group of patients should receive 12,000 to 16,000 units of antitoxin if treated during the first forty-eight hours,

12,000 to 24,000 if treated from the third to the sixth day. If the rash is still present after this period, but fading, 6000 to 12,000 units should ordinarily be sufficient, even though the pyogenic lesions are still active.

The third group of patients (Fig. 1c) comprises those with severe or potentially severe pyogenic or septic complications, such as severe purulent rhinopharyngitis usually with sinusitis, purulent otitis media, ulcerative tonsillitis, peritonsillar abscess, severe cervical adenitis, ulcerative stomatitis, mastoiditis, meningitis, thrombophlebitis, septicopyemia, etc. In the presence of one or more of these lesions early in the acute exanthematous stage of scarlet fever the degree of toxemia is greatly enhanced and often develops rapidly to a high point during the first forty-eight hours, 60 to 75 per cent showing severe toxemia and 15 to 30 per cent extreme toxemia. The severe toxemia may persist to the seventh or eighth day in this group, but ordinarily abates after this time, even though the septic lesions continue. Twelve thousand to thirty thousand units of antitoxin are required for these patients.

While no rigid scale of dosage can be formulated because of the many variables concerned, the following table will indicate the range of dosage ordinarily required during the exanthematous stage of the disease. As stated above, antitoxin treatment is not indicated after the rash has faded. The groupings are primarily made on the basis of the presence or absence of pyogenic or septic lesions, secondarily on the basis of total clinical severity.

APPROXIMATE DOSAGES OF ANTITOXIN REQUIRED IN THE TREATMENT OF SCARLET FEVER DURING THE EXANTHEMATOUS STAGE

Pyogenic or Septic Lesions Other Than Simple Tonsillitis	Total Clinical Severity	Units of Antitoxin (U. S. Hygienic Laboratory *)		After 7th Day Rash Still Present but Fading
		During First Week, Rash Present		
		Children	Adults	
None	Mild	6000	6000	....
	Moderate	6000	8000	....
	Severe	8000–12000	12000–16000	....
Moderate purulent rhinopharyngitis and cervical adenitis	Moderate	12000	12000–16000	....
	Severe	12000–16000	16000–18000	6000–12000
	Extreme	16000–18000	18000–24000	
Severe purulent rhinopharyngitis, sinusitis, severe cervical adenitis, otitis media, mastoiditis, ulcerative tonsillitis, sepsis, etc.	Severe	12000–16000	16000–20000	8000–16000
	Extreme	16000–24000	18000–30000	

* One unit neutralizes 50 S.T.D. of toxin. (If the unit value is based on one unit neutralizing 100 S.T.D. of toxin, divide each dosage by 2, e.g. 6000 units U. S. Hyg. Lab. = 3000 units when 1 unit neutralizes 100 S.T.D.)

THERAPEUTIC RESULTS

In order to interpret satisfactorily the therapeutic effect of scarlatinal antitoxin, it is necessary to keep in mind that one must distinguish between its effect on the specific toxic phenomena of scarlet fever on the one hand and its effect on the septic aspects of the disease on the other, since the two processes are of distinctly different nature. It has been shown by Blake and Trask, Park, Friedemann and Deicher, and many others, that antitoxin in proper amount is a specific and prompt cure for the essential toxic phase of scarlet fever, but that it benefits the pyogenic
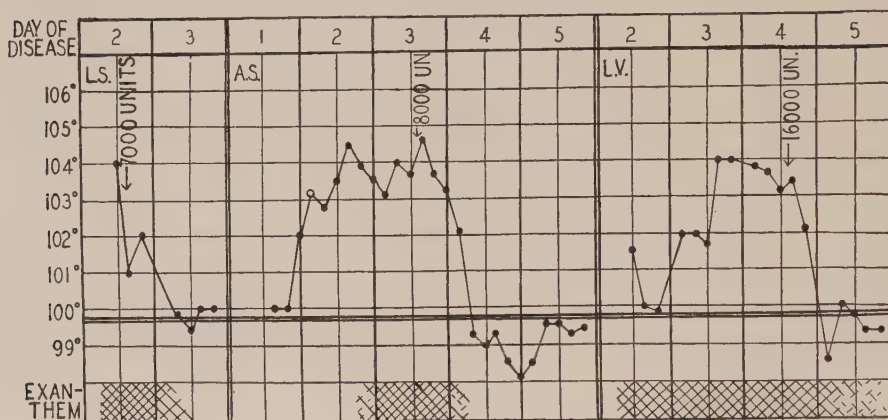
FIG. 2.—CRITICAL CURE OF UNCOMPLICATED TOXIC SCARLET FEVER BY ANTITOXIN INTRAMUSCULARLY.

L.S., age 25, moderately toxic. A.S., age 2½, severely toxic. L.V., age 24, severely toxic.

or septic aspects of infection with *Streptococcus scarlatinæ* only indirectly and only during the early acute toxic or exanthematous stage, presumably by curing the specific toxemia and thereby placing the patient in a position to overcome more readily the pyogenic complications. It is consequently important to remember that its efficacy depends upon the administration of a sufficient dose as early as possible in the disease, before the septic aspects of the infection have assumed a dominant rôle.

With early adequate treatment the effect of antitoxin is striking. In toxic scarlet fever uncomplicated by extension of the infection beyond the initial focus, the temperature and pulse rate return rapidly to normal, the rash promptly fades and all toxic symptoms subside. Within twelve to twenty-four hours convalescence is established. In patients with septic complications in whom the exanthem is still present, the specific toxic phenomena rapidly subside in response to treatment. The effect on the temperature and pulse will vary with the nature, duration and severity of the septic process. Except in the presence of very severe complica-

tions, there is usually a considerable drop in the temperature and pulse rate. Frequently, however, they do not become normal for several days or more. The course of the complications following antitoxin treatment varies considerably. Early septic processes frequently subside with remarkable rapidity. Those that have been present for several days before antitoxin is administered may subside gradually or run their natural course. In late cases with the rash fading they are little, if at all, influenced.

Desquamation is conspicuously diminished by early treatment. Patients receiving antitoxin within twenty-four hours after the first appearance of the rash show little or no desquamation. In patients treated late the usual degree of desquamation occurs.
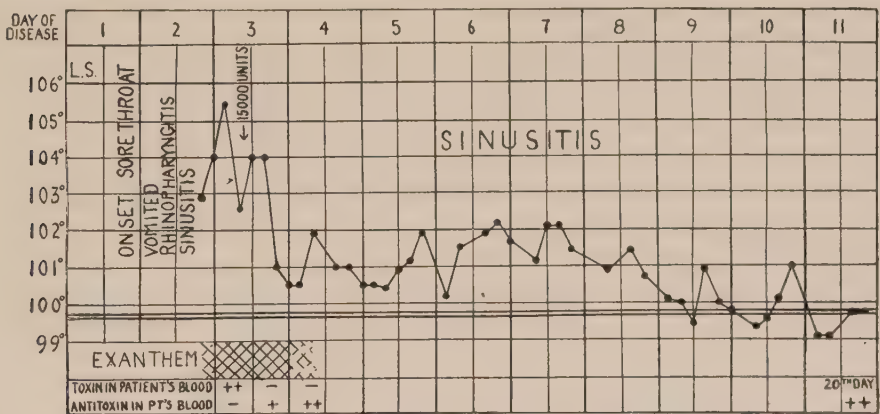
FIG. 3.—CRITICAL CURE OF TOXIC PHASE AND GRADUAL SUBSIDENCE OF SEPTIC COMPLICATION FOLLOWING ANTITOXIN IN TOXIC AND SEPTIC SCARLET FEVER.
L.S., age 21, severe.

Although it is impossible to present adequate statistical evidence at the present time, it is the expressed opinion of nearly all authors that early antitoxin treatment is effective in considerably reducing the incidence of late septic complications and of the sequelæ. That these can never be entirely eliminated by antitoxin treatment would seem probable, in view of the fact that pyogenic infections with *Streptococcus scarlatinæ* can occur in persons with an adequate antitoxic immunity and sequelæ can develop in persons who have a measurable amount of antitoxin in the blood. It is likewise impossible as yet to present satisfactory statistical evidence concerning the effectiveness of antitoxin in reducing mortality from scarlet fever, particularly as the reports available do not in most instances permit an accurate analysis of the time of treatment or of dosage in terms of units. It is clear, however, that the mortality in patients adequately treated on or before the third day is exceedingly small.

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CHAPTER XIX

THE MODERN TECHNIC OF VACCINATION

Henry L. K. Shaw

Definition.—Vaccination consists of the inoculation of the virus of vaccinia or cowpox into the tissues of the human body. The great importance of this disease is the fact that it protects an individual from smallpox and confers an immunity for an indefinite length of time. This procedure has nothing in common either in theory or practice with the misnamed "vaccinations" against typhoid fever, pertussis, etc., or with the stock or autogenous vaccines used in many infections.

History.—The protective property of cowpox against smallpox was recognized as early as 1713, by Salger, and in 1735 Fenster reported its value to the Medical Society of London. At this time variolation or the inoculation of smallpox was advocated by the medical profession as a preventive against smallpox. Generally, persons thus inoculated had only a mild attack of the disease; yet it was contagious and sometimes fatal to others and soon fell into disrepute. To Sir Edward Jenner, however, belongs the credit for popularizing the use of cowpox inoculation or vaccination as a preventive for smallpox and for his persistent zeal in promoting its practice. While a medical student, he started a series of investigations because of a chance remark by a farmer's daughter that she couldn't get smallpox because she had had cowpox. He made his first and historic inoculation on a country boy, James Phipps, on May 14, 1796, and two years later submitted his observations to the Royal Society of Physicians, but the paper was refused "lest it should lessen the reputation he had already gained and gave insufficient evidence of the value of the discovery." He then published the paper as a pamphlet entitled "An inquiry into the Causes and Effects of Variolæ Vaccinæ" which contained the findings after variolation of twenty-three cases.

This pamphlet has brought everlasting fame to the author, but even to this day there is bitter and bigoted antagonism to a simple procedure which has saved millions of lives and untold suffering among all the peoples of this world. To-day there is not a civilized or semicivilized country in the world where this procedure is not only practiced but made obligatory by the authorities.

Statistics prove the efficacy of vaccination without any shadow of doubt. Smallpox was a great scourge the world over before the introduction

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of vaccination. To-day it has been so entirely eliminated that we can scarcely realize the havoc it wrought in the human race. It was so prevalent that everyone was expected to have it at some time or other. The death rate in England during the eighteenth century as revealed in the "Bills of Mortality" shows that smallpox caused about one-twelfth of all diseases and that of all deaths occurring in persons under five years of age one-half were the result of smallpox. Before Germany established compulsory vaccination 6.65 per cent of all deaths were due to smallpox and after the use of vaccination this figure fell to 0.75 per cent. This applies only to the mortality, and the morbidity figures are even more convincing.

The records of the Surgeon General's office show that the mortality rate for smallpox among the soldiers in the Union troops during the Civil War was 37.2 per cent and many soldiers were never vaccinated. Vaccination was made obligatory during the World War and presumably every soldier was vaccinated. The mortality and morbidity rates for smallpox were negligible.

Epidemics in countries where there is strict compulsory vaccination are now unknown, but in England and in our own country, where vaccination is not strictly enforced and the whims of so-called conscientious objectors are respected, sporadic outbreaks occur at irregular intervals and the victims almost invariably are persons who have never been successfully vaccinated.

In spite of unquestioned corroborated evidence from all parts of the civilized world regarding the protective value of vaccination against smallpox, there still persist organized antivaccination societies whose object is to influence popular opinion against this great preventive method.

A statement made before the English Commission on Vaccination, in 1890, reveals the animus as well as the ignorance of the "antis." The speaker said that "vaccination is a gigantic delusion, that it has never saved a human life but that it has been the cause of so much disease, so many deaths, such a vast amount of utterly and altogether undeserved suffering that it will be classed by the coming generation among the greatest errors of an ignorant and prejudiced age." The question of personal liberty in regard to compulsory vaccination is made much of and one writer declared "that liberty is in my mind a far greater and more important thing than science." The claim has also been made that improved sanitary and housing conditions have been responsible for the decline in the number of smallpox cases and that vaccination has played no part in the decline of smallpox.

George Bernard Shaw is a notorious example of the prejudice and ignorance of those who publicly oppose vaccination. He joined in the protest of the antivaccinationists in 1914 against vaccination in the army. The following is an example from his fertile but prejudiced pen. "For years past the strain of countenancing such a proceeding, so gross, reckless, dirty

and dangerous as vaccination from the calf, has been growing unbearable to bacteriological experts. . . . Recent developments have shown that an inoculation made in the usual general practitioner's light-hearted way, without previous high-skilled examinations of the state of the patient's blood, is just as likely to be a simple manslaughter as a cure or prevention. But vaccination is nothing short of attempted murder." In the preface to "The Doctor's Dilemma" he denounced vaccination as "a horrible reversion to the most degraded and abominable forms of tribal ritual."

Our present security from the ravages of smallpox is apt to make people careless and indifferent in regard to vaccination, especially as the procedure is attended with some discomfort and inconvenience.

Virus.—The specific organism of vaccine, while not yet definitely identified, probably belongs to the class of protozoa. The so-called vaccine virus is obtained from a vaccinia lesion when in the vesicle stage. This has a slightly alkaline reaction and, besides, the vaccinia organism contains leukocytes and epithelial cells. This is called vaccine lymph. The vaccinia organism can also be obtained from the scab of a person who has been successfully vaccinated. On account of possible dangers of using the virus from human sources such as skin disorders, and certain diseases, the United States Government has taken control of the production of vaccine virus. Human virus is no longer used, as it was found that the virus obtained from vesicles produced after inoculation on healthy young calves was safest and best. The Government permits the use only of young healthy calves which are carefully examined and kept in quarantine for two weeks. When the vesicles appear they are curetted under surgical asepsis and mixed with a 50 per cent solution of glycerin. The virus is then kept in cold storage from two to twelve months, free from exposure to air and light. In the meantime the calf is killed and an autopsy performed to determine if it was free from all disease. A bacterial examination of the virus is made at frequent intervals and when no bacteria are present it is considered to be ripe and safe to use. As a further precaution the virus is injected into guinea-pigs to find if it is free from all pathogenic germs.

A small portion is drawn into capillary tubes which are immediately sealed. Some laboratories dip small ivory points into the material. These points are allowed to dry and thus are protected.

There have been many attempts to produce a sterile virus, and Noguchi at the Rockefeller Institute was able to grow it successfully on media made from the testicle tissue of young bull calves. The laboratory of the New York State Department of Health has prepared some potent virus by this method. It is safe to predict that the next step in the production of vaccine virus will be its sterile preparation in the laboratory and not in the stable.

The virus must be kept as cold as possible in order to retain its potency. Smallpox virus is not affected by freezing as is the case with other vaccines and serums. A vaccine of full potency should give 100 per cent "takes" when properly introduced on unvaccinated persons. If it is not kept at freezing temperature the potency becomes much less.

Time of Vaccination.—Vaccination of young infants is attended with less general reaction and fewer complications than in older children. The vaccination laws of Germany require that infants be vaccinated within the first year of life, unless ill or in poor health. When smallpox was prevalent the greatest number of cases occurred in young children. The writer had a case of smallpox in a three-weeks-old infant who contracted it in a maternity hospital from a patient thought to have chickenpox. When the diagnosis was established all the newborn infants were vaccinated without any bad effects. Early vaccination also tends to make less severe the secondary vaccination which is required when the child enters school.

It is not a matter of great importance during which season of the year vaccination is performed, as when done properly, the general reaction is not severe. It is best to avoid the extremely hot weather. Tight clothing must not be worn over the vaccinated area—a point that should be borne in mind when vaccinating in cold weather when more clothing is worn.

Technic.—The strictest asepsis must be observed in all the details of vaccination, and it must be considered a minor surgical operation. The left arm is the classic and favorite site for vaccination. The place usually selected for the introduction of the virus is at the insertion of the deltoid muscle. The only objection to this site is for cosmetic reasons, and some mothers object to scars on their daughters' arms. A vaccination scar should not be large enough to disfigure and should be considered a mark of honor, a "sanitary dimple," not a disgrace.

Generally, the reaction on the leg is more severe than on the arm. The leg is apt to become irritated from use in walking, from friction of the clothing, and from contamination by street dust. Many physicians refuse to vaccinate on the leg on account of these severe reactions. Persons who insist upon being vaccinated on the leg should be kept in bed for a few days when the vesicle appears, and should use the leg as little as possible until after the formation of the scab.

The skin over the selected site should be thoroughly cleansed with soap and water, but not irritated. It is dried with sterile gauze or absorbent cotton, and a few drops of alcohol, ether or acetone poured over the area. When this has thoroughly dried, a drop of the vaccine lymph is placed on the cleansed skin.

There are numerous methods of inoculating the virus. At one time special scarifiers were used which scratched a large area of skin unnecessarily. It is now recognized that only a very small abrasion is necessary,

and that the scratch must not penetrate through the true skin and must not produce bleeding. It is claimed that deep scarifications are apt to produce more severe inflammation. A blunt instrument, such as a jeweler's small screwdriver or a Pirquet Scarifier is convenient, as it will remove the epidermis without bruising the tissue and causing bleeding. It makes a very small point of entry which results in a small and inconspicuous scar.

J. P. Leake, of the United States Public Health Service, has suggested a new procedure which he terms the "pressure" method and which has been given a thorough trial by many physicians in thousands of vaccinations, and seems to be the simplest, safest and most satisfactory method yet advocated. The writer has used it extensively for over a year and is convinced that it causes less pain and disturbance in young children, produces less general reaction, makes a smaller scar, takes a shorter time to perform, and requires no dressings or attention until the appearance of the vesicle. The description of this method, as outlined by Leake, is as follows:

"The 'multiple pressure' method consists of a shallow, tangential pricking of the cleansed but not irritated skin with a needle, through a drop of smallpox vaccine, covering an area not greater than one-eighth of an inch (3 millimeters) in diameter. This gives little chance of accidental infection and the eruption is typical. The needle, which should be new, sharp and sterile, is not thrust into the skin but is held quite parallel or tangential to it, with the forefinger and middle finger of the right hand above the needle and the thumb below, the needle pointing to the operator's left. The needle should be held crosswise to the arm, so that the thumb of the operator may not be impeded by hitting the skin. The side of the needle point is then pressed into the drop about thirty times within five seconds, the needle being lifted clear of the skin each time. This rapid to-and-fro motion of lifting the needle and pressing it against the skin should be quite perpendicular to the skin and needle, and not in the direction of the needle. In this way the elasticity of the skin will pull a fraction of an inch of the epidermis over the point of the needle at each pressure, so that the vaccine is carried into the deeper layer of epithelial cells, where multiplication takes place most easily. If the skin has not been unduly rubbed in cleansing, and if the motion is entirely perpendicular to the needle, no signs of bleeding will occur, and all evidence of the punctures will fade out in less than six hours. Immediately after the punctures have been made, the remaining virus is wiped off the skin with sterile gauze, and the sleeve is pulled down, the whole operation of puncturing and wiping taking less than ten seconds. With strong vaccine a single pressure not infrequently gives a 'take.' Only six pricks or punctures were formerly advocated. Comparative tests showed this to be inferior to the scratch method in the percentage of successful 'takes.' By

the use of thirty pricks, this difficulty has been overcome and the percentage of 'takes' is as high as with any other safe method."

The time after the introduction of the virus before the local symptoms appear depends upon the virus, history of a previous vaccination and the personal immunity. An early or accelerated reaction which appears from two to four days after vaccination is called *vaccinoid*. It is found in persons who have been previously vaccinated and indicates a partial immunity. In a primary vaccination nothing is observed until the sixth
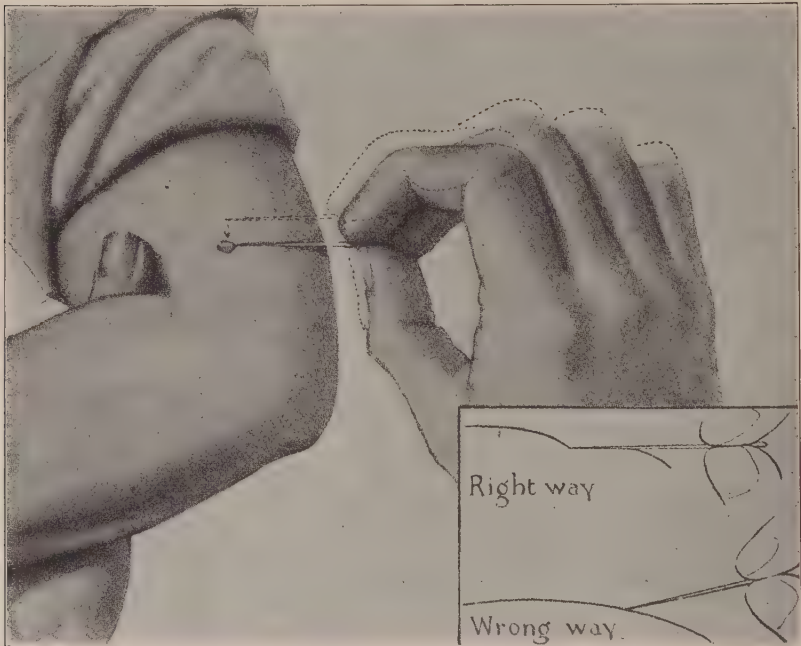
FIG. 1.—THE "MULTIPLE PRESSURE" METHOD OF VACCINATION.
Showing the rapid up-and-down motion of the needle, held by the hand at the right against the drop of vaccine on the arm at the left. (Courtesy of *Boston M. & S. J.*)

or seventh day. A zone of redness first appears about the site of vaccination; this becomes larger, and a distinct round hard papule forms in the center. In a few days this becomes vesicular and then pustular; the center becomes depressed or umbilicated and the periphery bulges and is more prominent. The zone of redness is called the areola and often extends several inches around the lesion. This areola is not the result of local infection with other organisms but is attributed to the reaction of the antibodies to the growth of the vaccine organisms. The lymph-nodes in the vicinity of the lesion and in the axilla or groin are frequently enlarged and may be quite painful.

There are generally some constitutional symptoms with the appear-

ance of the papule. There is a slight rise in temperature with slight chills, the sleep is disturbed and restless, and there are apt to be malaise and loss of appetite. These symptoms rarely last more than a few days and their intensity varies in different children.

On about the twelfth day after the appearance of the papule, the lesion begins to fade and the pustule becomes dryer. A scab formation starts in the center, the surrounding tissue becomes normal about the second week of the lesion, and the desiccation is completed. If left alone, the scab may not fall off until a week or two later. After the scab falls off, the scar appears smooth and red, but after a few months it becomes paler than the surrounding skin. It is usually pitted and has the appearance of being punched out with a sharp die. In some persons the center may become elevated and even keloid in character and such scars remain red for a long time. The condition of the scar gives some indication of the protection of the individual. Some believe that the size of the scar indicates the degree of protection. It is claimed by the advocates of multiple inoculation that the increased number of scars will prolong immunity. It is now the general and accepted opinion that it is not the size or number of the scars but the character of the scar itself that is important.

The bad arms and infections are the results of faulty technic, uncleanliness, negligence, and improper care. The use of "shields" of any form or shape is to be avoided. They constrict the capillary circulation around the wound and keep the lesion too moist and warm, making an excellent incubator for the growth of bacteria. The simplest and best dressing is several layers of sterile gauze placed over the lesion as a covering. This can be held in place by one or two narrow strips of adhesive plaster applied at least one inch above and below the point of vaccination. This protective covering shields the vesicle from injury as well as from infection. The itching may be almost unbearable at night; it is hard to keep young children from scratching and the finger nails are sure to carry infection. To relieve the itching, cold packs or a small icebag placed over the inflamed surface will give relief.

The vaccination sore and the blister should be kept dry. If this is not done, the exudate from the vesicle will adhere to the gauze and the scab will be torn off when the gauze is removed. When this occurs it should be cleansed with a boric acid or normal salt solution, dried with sterile cotton, and boric acid dusting powder applied. The gauze pad should be changed each day and the wound kept dry with unscented sterile dusting powder. Some physicians advise the use of a sterile vaselin or ointment applied on the gauze to prevent the possibility of the scab's adhering to the dressing.

Contra-Indications to Vaccination.—There are very few diseases or conditions which would justify non-vaccination in the presence of an epi-

demic or when a person has been directly exposed to smallpox. Patients with tuberculosis are not harmed by vaccination properly done. The only possible exception is acute lymphatic leukemia and diseases involving the lymphatic system. Contrary to popular opinion, failure of a vaccination to "take" does not prove natural immunity to smallpox. The reasons why a vaccination does not "take" are faulty technic or an impotent vaccine. If the first vaccination is unsuccessful, it should be repeated with fresh vaccine which has been kept cold.

Revaccination.—Immunity acquired after a successful vaccination varies in different persons. In some it may last through life but in the vast majority of cases it does not last more than ten years. A wise plan is to vaccinate in early childhood and again at puberty. During an epidemic or exposure, vaccination should be done at once.

Complications.—Any open wound presents possible dangers of infection. This can be avoided with proper care, and the infections and fatalities which occasionally occur after vaccination are avoidable and preventable. Tuberculosis, syphilis and skin diseases may show their initial symptoms shortly after a person is vaccinated, and the vaccination blamed and widely heralded by biased and ignorant persons. An insect bite or a pin prick not infrequently opens the way for an infection which may result fatally.

The strict preparation of bovine lymph and modern aseptic technic have greatly reduced the number of infections. Eczema, urticaria and furunculosis may occur with vaccination or be lighted up by it, but are not in any way due to the virus of vaccine.

Public Health Laws.—Vaccination is a public health measure and its purpose is the protection of mankind against the scourge of smallpox. In the United States each state enacts its own vaccination laws, and the opposition of the antivaccinationists and the strong political pressure they are able to exert in different states, make a uniform nation-wide law impossible. The Government regulates the production of the virus and has some control over vaccination through the regulation of interstate traffic. Vaccination is compulsory for anyone entering any branch of military or Government civil service.

CHAPTER XX

BLOOD TRANSFUSION IN SEPTIC DISEASES

Reuben Ottenberg

Indications.—The question of the treatment of severe septic condi-
tions by transfusion is one which has been much debated. The majority of
experienced clinicians are now convinced of the value of the method. On
the other hand, there are some who, like Coenen, think not only that
the transfusion has no value but is actually contra-indicated in septicemia.

The difficulty lies in the appraisal of the value of clinical evidence in
a group of diseases of diverse etiology and of extraordinarily varied and
unpredictable clinical courses. Many authors who have written most enthu-
siastically have presented dramatic accounts of clinical cures, but have
neglected to list their failures. Such work is of little scientific value. When
one remembers the long and arduous collection of statistical data which
has been necessary before the medical public has become convinced of
even so simple a thing as the therapeutic value of antipneumococcus serum,
one sees how hard it is to draw conclusions in so confused a field as
septic diseases. It must be acknowledged, therefore, that (except in one
or two very restricted fields, such as perhaps erysipelas) anything like
convincing scientific proof of the value of blood transfusion in septic sick-
ness is at present lacking, if not impossible of attainment.

The largest study of transfusions for septic diseases is that of Stetson
who presented sixty-eight cases from the material of Bellevue Hospital.
If one excludes the seven cases of bacterial endocarditis and four cases
which were moribund at the time of transfusion, there were fifty-seven
cases in which the author thinks there was a "fighting chance." Of these
thirty-one recovered (54 per cent). It is interesting to note the relatively
good results in cases of hemolytic streptococcus infections; of these, how-
ever, the majority—fourteen out of nineteen cases—were instances of
sinus thrombosis following mastoid disease, and nine of the fourteen cases
recovered (64 per cent); as the author himself points out, "the excel-
lent results in this type of case are due no doubt to the fact that the
surgeon is able to remove the septic thrombus." On the other hand, one
cannot help being struck by the poor results in general infections (blood-
cultures positive) with *Staphylococcus aureus*—only three recoveries out
of twelve cases. This is due, of course, to the great tendency of this organ-

ism once it reaches the blood stream, to form numerous secondary abscesses many of which are undiscoverable or inaccessible to surgery.

Other series of cases are those of Ottenberg and Libman, four recoveries out of ten transfusions, and Waugh twelve recoveries out of nineteen transfused for septicemia.

There is a good deal of evidence bearing on the clinical value of blood therapy. There are the many reports of individual clinicians who have again and again seen transfusions appear to be the turning point in profoundly sick people who up to that point had shown no tendency to recovery. (Bass, Ottenberg and Libman, Lindeman, Manges, Caplesco, Stetson, Hooker, Weston, Janes, Robertson, Brown and Simpson, Reimold and Kramer, and others.) Anyone who has seen many transfusions has some cases so striking that all who saw them were convinced that transfusion was of life-saving value. The author himself has seen at least ten such cases. While the collection of exactly comparable control cases not treated with transfusion is impossible, a study of the cases which died in spite of transfusion has usually shown some complication, such as numerous lung foci, meningitis, etc., which made recovery practically impossible.

Another reason for crediting the claims for transfusion is a consideration of the mechanisms of immunity and resistance to infection. The fact that normal individuals vary greatly in their resistance to different microörganisms, and that the person who has become seriously affected has in all likelihood less than the average capacity for developing resistance, suggests that normal blood may carry something that the patient lacks. Furthermore, in the less fulminant cases it is possible to carry out preliminary immunization of the donor to the patient's germ. While the evidence on the value of this is just as hard to evaluate as on the use of transfusion alone, the results seem encouraging enough to warrant further trial (Hooker).

Another factor that undoubtedly plays a rôle is the so-called "nonspecific protein reaction." A vast deal has been written about this; actually we know very little, and are not yet able to control the results or predict in what cases such reactions will do good. Nevertheless, there is no doubt that a great variety of different substances, which when injected into the tissues or blood stream are capable of producing febrile reactions, often have remarkable effects on the course of chronic infections. It has been shown that in such reactions there is a mobilization of antibodies (Steabben and others), of various ferments (Jobling and Peterson), and an increase of the alexin (complement) of the blood (Ronchi). Kinsella has shown that such reactions, whether occurring after blood transfusion or after the intravenous injection of so simple a thing as physiological saline solution, are capable of producing a transient (twenty-four hour) sterilization of a heavily infected blood stream. The fact that Kinsella's observa-

tions were made in a disease in which transfusion has uniformly been a failure in its effect on the ultimate outcome, namely, bacterial endocarditis, does not rob them of their significance. It seems probable that many of the most dramatic clinical results of transfusion in septic diseases have been due to this ill-understood factor of "non-specific reaction."

But perhaps the simplest way in which transfusion can be of use in septic cases is the most important, namely, in helping overcome anemia. Practically all the germs which cause the so-called "septic" infections are hemolytic in their effects, or have a toxic effect on the bone-marrow, and a rapidly progressive anemia is one of the most characteristic symptoms. There is no doubt that this anemia of itself is an extra weight on the already burdened resources of the body; it obviously entails extra work for the circulation and for the all-important bone-marrow. With transfusion it is one of the easiest of symptoms to overcome. This is one of the reasons why, as all experience shows, transfusions more often help in prolonged septic cases than in fresh acute ones. Another reason probably is that in the prolonged cases the body forces have already almost balanced the infecting forces, and it only requires a little extra help to swing the balance to the favorable side). This is also probably one of the reasons why all reporters give better results for transfusion in infants and small children than in adults; the amount of blood transfused in these tiny patients is, relative to the total blood-volume, much larger, so that anemia is more completely overcome.

Erysipelas in Infants
(Results of Robertson, Brown and Simpson)

Age	Not Transfused		Transfused	
	Died	Recovered	Died	Recovered
Under 1 month	5	1	1	1
1-12 months	13	14	0	12
Total	18	15	1	15
Per cent		44		93

There is one small group of cases in which the evidence for the therapeutic efficacy of blood transfusion is rather convincing, namely, erysipelas in infants. This is a very fatal disease; in the newborn it is usually stated to have a mortality of 100 per cent. Robertson, Brown and Simpson reported the above results. Neff has reported four additional cases in the newborn of which two recovered, and Schaffer and Rothman nineteen cases of which only four died and these were moribund when first seen. It should be noted that Robertson's infants received the exsanguination transfusions introduced by Bruce Robertson, which will be discussed

further below. The probability should also be kept in mind that infant's blood may lack some specific protective substance which adult's blood possesses.

On the other hand, there are certain types of septic diseases in which the results of transfusion have been discouraging in the hands of all workers. These are puerperal infections, pylephlebitis, cholangitis and multiple liver abscesses; it is seen that these are conditions in which surgical relief has not yet been sufficiently developed. In order that the body may eventually overcome a severe pyogenic infection it is necessary that local healing either be possible by the natural forces of the body or be made possible by surgical measures. In spite of this, further trials are warranted, particularly in puerperal infections in which occasional successes have been reported.

Methods.—Practically no two authors who have advocated transfusion for septic diseases have used the same methods. The points on which they have differed have been:

1. Whether to immunize donors beforehand and if so, how.
2. The method of transferring blood—whether by citration, syringe from arm to arm, or defibrination.
3. The frequency and volume of transfusions.

1. *Immunization of Donors.*—Many authors have advocated the preliminary immunization of donors by the usual method of serial injections of a vaccine prepared either from the patient's own organism or from a stock vaccine of the same type of organism (in order to save time). In bacterial endocarditis this has been as ineffective as all other methods of treatment. In staphylococcus septicemia Hooker reported an excellently studied series of six cases, all of which were considered practically hopeless at the start of treatment; four of them recovered. Hooker himself is doubtful, however, how great a rôle the immunization played, saying, "there is almost always a pronounced secondary anemia, and normal resistance to infection is very much impaired by this alone."

There is another type of so-called "immuno-transfusion" which was introduced by Wright and consists of the subcutaneous injection into the donor of a large dose (1000 million) of a non-specific vaccine (*Staphylococcus aureus*) four to six hours before the donor is used for transfusion. The procedure is based on the transient increased bactericidal power of the donor's blood after such injections. It is really an effort to take advantage of the non-specific protein reaction of the donor for the benefit of the patient. This procedure is not illogical but the small number of clinical cases so far reported do not lead to any conclusion as to its value. It seems worthy of further trial.

2. *Method of Transfusion.*—Many of those who have written on the subject have laid great stress on the importance of using one or another

technic. Thus those who practice the syringe method or one of its modifi-
cations believe that it is the best for infected cases, and condemn the
citrate method. Unger claims that citration of blood destroys complement
(alexin), increases the fragility of the red cells and diminishes opsonic
power. Mellon, Hastings and Casey, however, were not able to find any
of these effects. The post-transfusion chill and fever, which were claimed
by some to be more frequent after citrate than after other methods, are
often quoted as a disadvantage. But the careful work of Siebert showed
that most of the chills are due to some fever-producing substance in dis-
tilled water which has not been prepared with sufficient care. It is the
author's experience that with proper attention to this point the chills after
citrate transfusions are no more frequent than after syringe transfusions.
Robertson, whose results are certainly as good as anyone's, did his transfu-
sions by the citrate method.

On the other hand, Colebrook and Storer advocate defibrination of
the blood, claiming that this increases the bactericidal power, in spite of
the fact that it removes about one-quarter of the leukocytes. However, the
method of transfusion by defibrination introduced by Bischoff in 1835 has
been repeatedly tried and invariably given up because of real or assumed
accidents from embolism or thrombosis due to excess of fibrin ferment.
Probably the method is safe for small amounts of blood (it was used with
success by Moss) but unsafe for large amounts where the excess of throm-
bin is too great for the natural antithrombin in the circulation.

On the whole, balancing the claims of one school against the other,
and considering a personal experience in which many of the different
methods have been used, the author believes that it makes little difference
which method is used, provided the operator is sufficiently expert at it.

3. *The Amount and Frequency of Transfusion.*—All workers are
agreed that in septic diseases *repeated* transfusions are necessary. Many
do a preliminary phlebotomy and then transfuse an amount of blood larger
than that removed from the patient. Robertson does this repeatedly at
each sitting so as to replace as large a part of the patient's blood with
normal blood as is possible. For adults he has to use several donors; in
infants and small children he is able to replace practically the whole of
the patient's blood. The extraordinary results in children seem to warrant
further trials of this method for suitable cases in adults also.

In children Robertson in his "exsanguination transfusion" (as
described by Cross) first draws from the donor and citrates about twice
as much blood as the estimated blood volume of the patient. Thus he esti-
mates about 35 c.c. of blood per pound of the child's weight and for a
10-pound baby estimated to have 350 c.c. of blood draws 700 c.c. of
blood from the donor. He then removes 80 to 100 c.c. of blood at a time
from the child and replaces it at once with an equal volume of the citrated
donor's blood. This is repeated until all of the prepared donor's blood

has been injected, except that the last injection is always larger than the last phlebotomy. For drawing blood from the child he uses the external jugular or the femoral vein or, in small infants, the longitudinal sinus. For the introduction of blood he exposes the saphenous vein over the internal maleolus.

Robertson's method has three advantages: It removes circulating toxic products and bacteria, it replaces most of the patient's blood with healthy blood, it completely overcomes anemia. On this last point Libman and Ottenberg pointed out many years ago how small an effect can be produced on a severe anemia by an ordinary transfusion. Thus their simple calculation showed that even by transfusing so unusually large an amount as 1250 c.c. of normal (100 per cent hemoglobin) blood into a man of 114 pounds weight with a hemoglobin of 30 per cent one could only hope to raise the hemoglobin to 50 per cent. It is easy to calculate that by using the same amount of blood with the Robertson type of phlebotomy one would raise the hemoglobin considerably more.

It is for this reason probably that those who do not employ "exsanguination transfusion" have found the best results to be obtained by doing moderate sized transfusions (300 to 500 c.c. for adults) every two or three days. When this is done the body removes a certain amount of the transfused plasma from the circulation after each transfusion, so that the concentration of red cells progressively increases and, so far as the anemia is concerned, a similar effect is obtained to that of the "exsanguination transfusion."

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CHAPTER XXI

TREATMENT OF SYPHILIS

John H. Stokes

The recent advances in syphilotherapy may well be considered under the following heads.

BISMUTH

Bismuth was introduced into the treatment of syphilis through the work of Sazerac and Levaditi, in 1922, and has come to occupy an increasingly important place in therapy. It is generally accepted that as a spirillicide bismuth is inferior to the arsphenamins but definitely superior to mercury. Milian represents the relative therapeutic activity of antisyphilitic drugs as follows: Arsphenamin 10, bismuth 7, mercury 4. The potassium tartrobismuthate was the salt originally advocated for the treatment of human syphilis, but the drug is now marketed in several therapeutically effective forms including the metal itself, the salicylate, hydroxid and iodoquinate. Warren has emphasized the variability of bismuth content in the same or various salts of bismuth in common use, a fact which should induce the physician to critically discriminate in the selection of these drugs for the treatment of syphilis. No salt containing under 50 per cent metallic bismuth can be expected to give full therapeutic effect.

Kolle's experimental work showing that the action of bismuth is more inhibitory than actually curative indicates the inadvisability of using it as a substitute for the arsphenamins. Jeanselme has recently expressed the belief that the substitution of bismuth for arsphenamin in French practice is in part responsible for an increasing incidence of syphilis in France. Bismuth finds its chief field of usefulness as a substitute for mercury and as a new angle of approach in Wassermann-fast and relapsing infections. It must be reëmphasized, however, that sufficient time has not yet elapsed for final evaluation of bismuth in the therapy of syphilis. Anwyl-Davies has definitely shown that bismuth is less effective than mercury in reversing the Wassermann reaction. The wholesale adoption of bismuth at the sacrifice of a potent and dependable drug like mercury seems hardly justified in the light of present knowledge.

The rate of elimination of bismuth varies with the compound and the vehicle, the routes of elimination being the same as for mercury. Fetor

followed by stomatitis and often associated with a blue line on the gums is the commonest complication; it can very largely be prevented by proper mouth hygiene. Intramuscular injection is the most generally used method of administration, extreme care being taken to prevent escape into the blood stream because of the fatal result which may follow such an accident. Pain and induration at the site of injection are at times unavoidable, but demand careful recheck of every detail in the technic of administration. Diuresis and slight renal irritation occur in many patients on bismuth therapy, but permanent injury to the kidney has not been noted.

The bismuth salts in common use are administered in doses of 0.2 gram at intervals of four to seven days for a series of ten to twenty injections. The incorporation of a suitable local anesthetic seems to lessen the incidence of discomfort at the injection site. Courses of bismuth may be used to advantage in alternation with those of mercury. Prolonged courses of bismuth, 0.2 gram weekly for forty to sixty injections, seem to be specially advantageous in cases presenting arsenic fastness or fixed positive Wassermann reactions.

NEWER ARSENICALS

It must not be inferred that arsphenamin has been replaced by the preparations about to be mentioned. The new compounds constitute a different angle of attack but each has its own limitations as well as indications.

Bismuth Arsphenamin Sulphonate.—This new synthetic containing 23 to 25 per cent bismuth and 12 to 15 per cent arsenic was originated by Raiziss and has been subjected to extended clinical trial by Stokes and Chambers, O'Leary, and others. The ultimate effect of this drug, unaided, in early syphilis appears to be equal if not superior to that of modern intensive combined treatment with other drugs. It constitutes another angle of attack in arsenic- and mercury-fast patients, while the absence of therapeutic shock associated with its use makes it a valuable drug in the treatment of cardiovascular syphilis. It is administered twice weekly in doses of 0.2 gram by the intramuscular route. Four courses of twenty injections each, with or without a short rest interval between courses, constitutes the average amount of treatment necessary. As a move toward simplification and increased effectiveness in the therapy of early syphilis, this new compound has much to commend it.

Sulpharsphenamin.—Sulpharsphenamin, chemically closely related to neo-arsphenamin, combines the desirability of intramuscular administration with the highest penetrating power for the nervous system of any of the spirillicidal drugs, while therapeutically it is at least the equal of neo-arsphenamin. It is administered intramuscularly in doses of 0.4 to

0.6 gram every five to seven days for a series of eight injections per course. The higher incidence of exfoliative dermatitis associated with its use and the not infrequent reports of the development of aleukemia hemorrhagica, with its high mortality and clinical picture of an aplastic anemia, have been deterring factors to its more general adoption. Personal experience with the latter complication alone has induced me to practically abandon the use of sulpharsphenamin except in selected cases. Bismuth arsphenamin sulphonate would seem to be a worthy substitute.

TREATMENT OF EARLY SYPHILIS

The principles of treatment in early syphilis remain unchanged, the recent advances being confined to the introduction of bismuth into the treatment program and the acceptance of bismuth arsphenamin sulphonate alone as adequate therapy. We have also come to a new realization of the fact that syphilis must be worn out, not knocked out, and consequently do not follow so strictly the weight dose ratio. Personally, I seldom find it necessary to give more than 0.45 gram arsphenamin or 0.6 gram neoarsphenamin. Some would entirely substitute bismuth for mercury but we do not as yet possess sufficient proof of the therapeutic efficiency of bismuth to justify such a move. The alternation of courses of bismuth with those of mercury in the treatment program seems desirable. Continuous treatment without rest intervals for the first twelve to eighteen months is still considered a necessary part of adequate therapy in early syphilis.

It was formerly my practice to examine the spinal fluid of all patients with early syphilis within the first two weeks of treatment and at least two or three times during the ensuing year. In view of the fact that the initial high percentage of abnormal fluids is so greatly reduced by time and treatment, I have come to believe that one may safely wait to do the first spinal puncture until about the sixth month of the infection after the patient has had intensive arsphenamin treatment combined with either mercury or bismuth. Abnormal fluids at that time demand more intensive therapy and periodic reëxamination.

TREATMENT OF NEUROSYPHILIS

Most of the non-specific agents employed in the treatment of syphilis to increase systemic resistance against disease involve the induction of fever either by inoculating the patient with the plasmodium of tertian malaria, the spirochetes of relapsing, or rat-bite fever, or the injection of foreign proteins as typhoid vaccine.

Malaria Therapy.[1]—The malarial treatment, based on the work of

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[1] For fuller details regarding this form of treatment the reader is referred to Bunker's article in this volume.

Wagner-Jauregg, in 1918, has been the subject of much critical study. While certain phases of tabes in properly selected cases respond in part to this therapy, it finds its chief field of usefulness in paresis. About 2 c.c. of blood from a patient with tertian malaria is obtained during or immediately after an attack of fever and injected subcutaneously into the subject. After an incubation period averaging two weeks, chills and fever develop and the infection is allowed to progress through ten to fifteen paroxysms before termination with quinin, provided no contra-indications develop or daily blood examination does not show more than 10 per cent of the erythrocytes invaded by the plasmodium. O'Leary reports a primary mortality of 5 per cent. In early paresis, the reported remissions of cases observed in this country do not exceed 50 per cent and in general, clinical recoveries are noted in approximately 30 per cent, while an additional 20 to 30 per cent show distinct improvement. Good results are proportionate to the height of the fever developed as well as the clinical phase of the infection when treatment is instituted. The enforced isolation of patients undergoing this therapy and the risks and complications involved militate against its general adoption, and make it a method of last resort for expert decision and supervision.

Tryparsamid.—Tryparsamid prepared by Jacobs and Heidelberger of the Rockefeller Institute is a welcome addition to modern neurosyphilotherapy. The drug contains 24 per cent arsenic in pentavalent form. While only feebly spirillicidal, it is a potent stimulator of resistance and has a high degree of penetration for the central nervous system. Its use in the therapy of syphilis is restricted to late neurosyphilis without marked mental and physical deterioration. Early paresis or resistant neurosyphilis of the paresis sine paresi type is influenced most favorably. Tabes dorsalis is not strikingly improved under tryparsamid although crises and lightning pains may respond to this therapy when other measures have failed. Disturbances of vision stand out as the chief untoward effect of tryparsamid therapy, but the risk of this complication is less serious than at first believed. Tests for visual acuity and perimetric fields should be routinely carried out for the first six or eight injections, after which time injury to sight seldom occurs. Fundus examination alone is not sufficient to warn of impending loss of vision. Even when disturbances in vision occur the drug can often be cautiously resumed after a rest interval. The drug is administered in doses of 1 to 3 grams at weekly intervals. Solomon has shown the wisdom of giving continuous treatment over a period of from two to three years. The drug is given intravenously by syringe technic, 3 grams being dissolved in 10 c.c. of sterile distilled water.

Intraspinal Therapy.—While intraspinal therapy is still useful in selected cases of low tabes, primary optic atrophy, and infections resistant to other agents, there is a growing tendency to supplant it by malarial

therapy and tryparsamid. Its use has always been a matter for expert decision and in cases of doubt it would seem advisable to resort first to simpler and more practical methods of treatment.

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CHAPTER XXII

PREVENTION AND TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER

R. R. Spencer

GENERAL CONSIDERATIONS

Definition.—Rocky Mountain spotted fever is an acute specific, non-contagious, tick-borne disease, endemic in the northwestern United States. Clinically, it closely resembles typhus fever and is characterized by an onset with chill, continued fever, severe headache, pains in the bones and muscles, and a macular and sometimes maculopapular eruption which appears on about the third day of fever, first on the wrists, ankles and back, and then over the whole surface of the body.

Etiology.—The causative agent of Rocky Mountain spotted fever has never been successfully cultivated on artificial media, and, therefore, its exact nature is still obscure. Minute pleomorphic, Gram-negative, intracellular organisms (so-called Rickettsiæ) have been described by Wolbach in the tissues of infected ticks and in sections of pathological material from human cases, and the name *Dermacentroxenus rickettsi* proposed for them. The association of these organisms with the infection of Rocky Mountain spotted fever has been generally confirmed, but some investigators believe that the virus passes through phases and may assume still other forms not yet demonstrated, since highly infected ticks may be often found free of rickettsiæ. In normal ticks also rickettsiæ are frequently seen, and it is difficult to distinguish these from those associated with the disease; as a rule, they can be demonstrated more easily in the tissues of ticks than in the infected animal. The virus is not filtrable through even the coarse Berkefeld filters.

The Disease in Nature.—The infection in man is purely accidental and secondary, and man plays no part in the maintenance of the disease in nature. In this respect it resembles bubonic plague and stands in contrast with yellow fever, malaria, typhus fever, or any insect transmitted diseases in which man is an essential host. The small, wild rodents (rabbits, ground squirrels, woodchucks, chipmunks, etc.) acquire experimentally a mild infection which is rarely fatal and it is assumed this is what happens in nature since many immune rodents have been encountered. These animals thus become more or less healthy carriers and undoubtedly are largely

responsible for the continuation of the disease. Large numbers of premature ticks (larvæ and nymphs) of the species *Dermacentor andersoni* can be infected by feeding on these rodents during the acute stage of the disease. About half of the batches of eggs from infected female ticks will be found infected and the seed ticks or larvæ hatching from these eggs will also retain the infection. The large domestic animals (horse, cow, sheep and dog) and the large wild animals (elk, deer, and mountain goat) are immune.

In the majority of human cases the disease is contracted through the bites of the adult wood tick, *Dermacentor andersoni,* which is active from March to July each year and thus determines the seasonal prevalence. The infection may also be contracted by hand picking of ticks from domestic stock. If ticks are thus mashed between the fingers, or the tick feces handled, infection is likely to occur, since the virus has been found to penetrate even the unbroken skin. Ten cases among laboratory workers have occurred without history of tick bite and presumably by handling infected material.

The rabbit tick, *Hæmaphysalis leporis palustris,* also harbors and transmits the infection from rodent to rodent. This tick, however, never bites man.

PREVENTION

No completely successful method of prevention has yet been devised. However, investigations have been carried out along three main lines: First, a study of the disease, as it occurs naturally in ticks and animals, with the object of developing some practical method of tick or rodent destruction; secondly, the introduction of a tick parasite for the purpose of reducing the normal abundance of ticks to a point where the disease would cease to propagate itself, and, finally, laboratory studies of the behavior of the virus in ticks and experimental animals with the object of developing a preventive vaccine or serum.

For many years the Montana State Board of Entomology has practiced rodent destruction and dipping of domestic stock in a highly infected area of western Montana. While the results have not been entirely satisfactory, case incidence has decreased and the number of wild rodents and ticks near homesteads has been markedly reduced. These measures are recognized merely as a means of control and do not reach the reservoirs of infection among the wild animals and ticks in the thousands of square miles of uncultivated mountainous country.

Rodent Control.—Poisoned grain is used for the destruction of small rodents, chiefly ground squirrels. The work is carried on in the early spring when the animals first appear from hibernation. About one teaspoonful is placed usually on the surface of the ground at the rear of the rodent's hole or burrow. It should be either spread out over the ground or

placed in a small shallow depression where it will be accessible to the rodents but not attract the attention of large domestic stock.

The following formula is used by the Montana State Board of Entomology:

Crushed whole oats	40 quarts
Strychnin	5 ounces
Saccharin	5 drams
Starch (gloss)	2½ pounds
Sodium bicarbonate	5 ounces
Water	5 pints
Molasses	4 pints

The dry materials (oats excepted) are mixed together thoroughly and one quart of water added and stirred until the starch is dissolved. The balance of the water (1½ quarts) is added to the slightly warmed molasses. The dry materials are then mixed in thoroughly with the molasses and water. This mixture is poured over the oats and mixed rapidly with the hands. Rubber gloves should always be worn and the hands carefully washed when the operation is completed. The grain mixture is then spread on canvas or muslin racks until it is thoroughly dry.

Dipping of Domestic Stock.—This procedure is carried out to kill the adult ticks. The animals should be dipped at least twice a month from March 15th to May 15th. The method has not worked very satisfactorily, partly because of the difficulty of getting the range stock to the dipping vats, which are placed about twelve miles apart, and partly because dipping, during the cold inclement weather which occurs so frequently at this season, has sometimes killed the stock.

The dipping vats hold about 2,500 gallons, and the Bureau of Animal Industry boiled dip has been generally used:

Sal. soda (washing soda)	24 pounds
White arsenic (arsenic trioxid)	8 pounds
Pine tar	1 gallon
Water	500 gallons

About 125 gallons of water are heated to near the boiling point in a large mixing pan. The soda is added slowly and, after again coming to a boil, the white arsenic is also added, slowly stirring constantly. The mixture is then cooled to 140° F., the tar added, and the whole mixed thoroughly and poured into the water-filled vat.

Attempts to control the disease have not been made outside of Montana, and no one control program would be applicable to all areas because of the widely different conditions. An adequate control of the disease, it is now known, is a far more difficult problem than the control of insect-borne diseases, such as malaria and yellow fever. This is due, chiefly, to

the multiplicity of susceptible rodent species; furthermore, to the fact that the insect vector is not limited in its feeding habits to one host, and, finally, to the fact that man plays no part in the maintenance of the condition in nature.

Tick Parasites.—In 1926, R. A. Cooley, Montana State Entomologist, introduced the tick parasite, *Ixodaphagus caucurtei,* which was obtained from Brumpt, of the University of Paris, who had recommended its use in the control of the spotted fever tick. These parasites belong to the order Hymenoptera. The adults are very active minute black insects, measuring about one millimeter in length. The females pierce the nymphal ticks with their ovipositors and lay their eggs. The eggs hatch into maggots which feed upon the substance of the tick and finally destroy it. It is extremely rare for a parasitized tick to survive. In over six months of continuous rearing not a single parasitized nymph has lived.

The maggots develop into pupæ and, finally, adult insects emerge from the shell of the dead tick. After copulation the females are again ready to lay eggs. The complete cycle occurs within about six weeks in the usual summer temperature.

These parasites have been found to survive the winter under natural conditions in Montana and Massachusetts, and in the summer of 1928 over 100,000 were released in various tick-infested areas throughout Montana. It will be several years, however, before their effectiveness in the reduction of ticks and the resultant effect upon spotted fever infection can be estimated.

Personal Care.—The most effective measure of prevention is, of course, the avoidance of the known infected areas, especially during the spring and early summer. For those whose occupation compels them to enter these areas, such as lumbermen, forest rangers, surveyors, etc., it is recommended that they examine their clothing and bodies for ticks at frequent intervals, at least twice daily. Fortunately, the tick does not attach itself at once but crawls around for some hours, apparently seeking a spot where it will be protected from rubbing. It usually attaches in the hairy portions of the body. As a rule, ticks do not infect their host for several hours after attachment; therefore, the sooner ticks are removed, the better. After removal of the tick the spot should be cauterized with luna caustic or nitric acid.

Tight-fitting leggings or puttees should be worn in the infected areas. In this way ticks are forced to crawl up the outside of the garment and are thus more easily detected on the clothing or seen or felt upon reaching the neck.

Prophylactic Vaccination.—Rocky Mountain spotted fever is a disease that confers a lasting immunity upon individuals that recover and, therefore, one might reason that attenuated virus, provided it could be obtained in sufficient concentration, should confer some protection. With

this thought in mind, Spencer and Parker have recently developed a vaccine prepared from the ground viscera of highly infected ticks in which the virus content was found to increase tremendously following tick feeding. The harmlessness of a vaccine prepared from an insect host was at first doubtful. However, the material has now been given to more than four thousand people in Montana, Idaho and Wyoming, with no harmful effects, but with encouraging results as to its usefulness.

The vaccine is prepared in the following manner:

Wild ticks collected in the field are permitted to feed on infected guinea-pigs after the onset of the fever, placing about seventy-five ticks in a wire gauze capsule fastened to each animal. After three days of feeding the ticks are removed and placed in cold storage (40°-45° F.), where they may be kept for several months. Upon removal, the ticks are again fed upon normal animals for five to six days. This second feeding produces a tremendous increase in the number of minimal infectious doses of the virus per tick. For routine purposes, it is not necessary to determine this dosage as was formerly done by the graded injections of the live tick-virus suspensions.

The partly engorged ticks (males and females) are now ground in a mechanically operated porcelain mortar and pestle with fine quartz sand and a small quantity of physiological salt solution to which has been added 1.6 per cent phenol and 0.4 per cent formalin. After thorough grinding, the whole mass is transferred to a large stock bottle, and an additional amount of the salt solution and preservative is added until the concentration reaches, but does not exceed four ticks per c.c. After standing for forty-eight hours, during which time the preservatives will precipitate most of the tick protein, an equal volume of physiological salt solution is added. This dilutes the preservatives to 0.8 per cent phenol and 0.2 per cent formalin, at which stage the material is kept for seven days at room temperature. This has been found a sufficient period to kill most extraneous organisms, including sporebearers.

The suspension is then diluted once more by again adding an equal volume of salt solution, which final dilution will contain 0.4 per cent phenol, 0.1 per cent formalin, and the killed virus equivalent of one tick per c.c. The sand, chitin, and precipitated tick protein is now removed by centrifugation and the remaining clear, amber-colored, supernatant fluid is ready for the final containers. Occasionally some precipitate forms after placing the centrifuged vaccine in the final containers. This is disregarded for it does no harm when injected and besides contains protective qualities. In fact, the discarded heavy precipitates from many lots may be combined and resuspended in sterile salt solution, again cleared by centrifugation, and the clear supernatant fluid still found to possess splendid protective qualities. A number of such lots have been so made and used in human vaccination.

The vaccine is finally tested for potency by inoculating six guinea-pigs subcutaneously with 1 c.c. each. After twelve days the animals are given a test dose of 1 c.c. of guinea-pig blood-virus intraperitoneally. If four of the six animals do not develop a fever above 39.6° C. for more than two days, and show no symptoms of spotted fever, the vaccine is considered suitable for human use. Sterility tests are made in accordance with the Hygienic Laboratory standard for biological products.

It is recognized, of course, that an arbitrary standard of potency of this kind involves several variables, and the potency of any two batches of vaccine is only approximately the same.

The accompanying table gives the results of two years' vaccination among a group of 557 sheep herders in a small area in southern Idaho, and similar tests among highly exposed laboratory workers and residents of an infected area in western Montana over a period of four years.

ROCKY MOUNTAIN SPOTTED FEVER

TESTS ON PROPHYLACTIC VACCINE

SOUTHERN IDAHO	WESTERN MONTANA
Sheepmen in given area...... 557	A. Highly exposed laboratory and field workers 75

	Vaccinated	Not Vaccinated		Vaccinated	Not Vaccinated
Number	193	364	Number	59	16
Fever cases	1	22	Fever cases	8	4
Deaths	0	0	Deaths	1	4

B. Residents in exposed area...1208

	Vaccinated	Not Vaccinated
Number	496	712
Fever cases	4*	9†
Deaths	0	7

* Cases exceptionally mild.
† Cases exceptionally severe.

Duration of Protection.—The vaccine has not yet been used extensively enough and over a sufficient number of years to determine its exact field of usefulness. It seems clear, however, that the duration and degree of protection vary greatly and in some cases immunity may not last longer than one season. It is, therefore, recommended that two doses of 2 c.c. each of the vaccine be given subcutaneously at five-day-intervals and repeated each year before the beginning of the tick season. Each successive year's vaccination seems to increase the degree of immunity.

Reaction from the Vaccine.—The subcutaneous administration of the vaccine produces, as a rule, only local symptoms of redness, swelling and itching. Occasionally there is headache, slight fever and general malaise for twenty-four to forty-eight hours. In rare cases an urticarial rash with intense itching may follow but such cases have cleared up without serious consequences.

Manufacture and Distribution.—At present, the vaccine is manufactured by the United States Public Health Service at Hamilton, Montana, and is distributed to physicians free of charge with full directions for its use. The demand for the material is probably not large enough to make its production commercially feasible, and the services of highly trained workers are required. Because of the great danger involved, immune individuals are employed wherever possible. Three immune individuals who had very mild attacks of spotted fever, following vaccination, are now employed in tick-rearing which is the most dangerous phase of the work.

TREATMENT

General.—It is highly important that the patient be put to bed at once in a quiet room, and not moved. Every ounce of strength should be conserved and the heart saved from unnecessary work since exhaustion is always a marked symptom. The failure of the heart muscle, as evidenced by a thready and rapid pulse, is often the first indication of a fatal outcome. For this reason a course of digitalis therapy should be started early.

Veronal or some mild soporific should be given for insomnia and for the low grade delirium. These are often quite troublesome symptoms. Special care should be taken to keep the lips, tongue and buccal mucous membrane moist with a suitable mouth wash, as they become very dry and parched, if neglected.

Cold or tepid sponges may be given every three or four hours for the fever, but it is best to avoid antipyretics because of their depressing effect upon the heart. Liquids in the form of lemonade or orangeade should be given liberally, and an enema each morning if indicated.

The diet should be light, nutritious and easily digestible.

Specific.—No specific drug has been found, nor has a curative antiserum been developed. Such agents, as tried so far, seem to be of as little value in Rocky Mountain spotted fever as in so many other diseases of this class in which the virus occurs in concentrated amounts not only in the blood but intracellularly throughout all the body tissues. However, the serum from recovered animals will prevent infection if given to experimental animals before the onset of symptoms.

Herbert Hayward of Hamilton, Montana, has tried transfusions from recovered patients to several of his cases without apparent benefit.

Quinin hydrochlorid, salvarsan and mercurochrome have been used

extensively without convincing evidence as to their value. In our hands, these drugs as well as mercury bichlorid, atoxyl, sodium bismuth tartrate and manganese chlorid have failed to show any beneficial effect upon experimental animals. Animals receiving such drugs in non-fatal doses have invariably died earlier than the non-treated controls.

Numoquin hydrochlorid (Merk), used in the treatment of pneumonia, has lately been recommended. In the treatment of experimental animals we have not found it of any value.

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CHAPTER XXIII

THE PROPHYLAXIS AND TREATMENT OF AMEBIASIS

Charles F. Craig

Definition.—By the term "amebiasis" is understood an infection with *Entameba histolytica*,[1] a species of ameba parasitic in man and the cause of amebic dysentery. The importance of the prophylaxis and treatment of infection with this parasite can hardly be overestimated as it has been shown by the writer as well as by several other observers, that infection with this organism not only may be followed by a severe form of dysentery, which may cause the death of the patient, but that it more commonly produces symptoms connected principally with the digestive and nervous systems, which may result in long-continued ill health and often a condition of semi-invalidism. In addition, many individuals harboring *Entameba histolytica* do not present any symptoms of the infection but may at any time develop such symptoms, and these individuals are the principal agents in the transmission of the infection from man to man. Such individuals are "carriers" of *Entameba histolytica* and are a constant menace to those with whom they associate, and, together with those presenting mild and atypical symptoms, furnish a most important problem in the prophylaxis of the infection.

Prophylaxis of Amebiasis.—In order that we may intelligently consider the prophylaxis of infection with *Entameba histolytica* it is necessary that one has a clear conception of the life-history of the parasite, its method of transmission, its resistance to various physical and chemical agents, and the best methods of applying what knowledge we have regarding these factors in the prophylaxis of this infection. Before considering these subjects it should be stressed that the old conception that *Entameba histolytica*, together with the form of dysentery which it causes, is limited to tropical and sub-tropical regions is absolutely false, for the parasite has been found to be present in all localities in which surveys have been conducted. It is probably true that in temperate regions throughout the world at least from 6 to 8 per cent of all individuals are infected with this parasite and so far as the United States is concerned, it has been

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[1] In this chapter the spelling *"Entameba histolytica"* is used for editorial reasons, but it should be understood that the proper spelling of this name, according to the International Committee on Nomenclature, is *Endamœba histolytica,* and this is the proper zoölogical name of the parasite.

repeatedly shown by careful surveys that from 8 to 10 per cent of the population is infected and that the percentage is even higher in certain regions in the southern portion of our country. It has also been conclusively shown that amebic dysentery frequently occurs in the United States, especially in the southern states, and that it is by no means infrequent in the northern portion, while amebic diarrhea and the other symptoms caused by the parasite are frequently observed in all parts of the country. The writer has found that in his experience at least 50 per cent of the so-called "healthy carriers" of *Entameba histolytica* present symptoms of the infection and that practically 10 per cent of individuals from all parts of the United States harbor this parasite. Therefore, it is evident that the prophylaxis of the infection is a matter of great importance both from economic and health standpoints.

Life-Cycle and Relation to Disease.—*Entameba histolytica* is a parasitic ameba living in man and has three well-defined stages in its life-cycle: a vegetative stage, in which it is motile and divides by simple division into two amebæ; a precystic stage, in which it is immotile; and a cystic stage, in which it is immotile. In the cystic stage it is surrounded by a resistant cyst wall, and the nucleus divides into four nuclei prior to excystation. The natural habitat of the organism is in the lumen and tissues of the large intestine, the vegetative, or motile, forms occurring in both localities, while the cysts are found only in the lumen of the intestine. In the tissues of the intestine, or, when conditions are favorable, within the lumen of the bowel, the vegetative, or motile, forms divide into two daughter organisms, and this division continues indefinitely as long as the organisms are in the tissues or under favorable conditions. When conditions become unfavorable for vegetative existence the parasites encyst and no further division occurs in the intestine, although within the cysts the nucleus divides into four daughter nuclei. The cysts are the infective agents and are voided in immense numbers in the stools of the infected individuals. Reaching food or drink, the cysts are ingested by an individual, pass through the stomach and small intestine, and in the upper portion of the large intestine liberate the four-nucleated amebæ which immediately divide into four daughter amebæ. These are motile and if conditions are favorable, proceed to invade the tissues of the intestine, where the vegetative, or motile, stage of development is resumed. It is probable that the motile forms also multiply in the lumen of the bowel and invade the tissues when conditions are favorable. The precystic forms occur in the lumen of the bowel and represent simply vegetative forms which have rounded up, lost their motility, and are preparing to encyst. There is no proof that the cysts ever liberate the four-nucleated amebæ prior to passing out of the body and ingestion by a new host, although some authorities believe that this may occur under favorable circumstances.

It has been shown by numerous authorities that the motile, or vegeta-

tive amebæ, are unable to pass through the stomach, if ingested in contaminated material, as they are unable to resist the acid of the gastric juice, so that this form of the parasite is not infective. On the other hand, it has been shown that the cysts are very resistant to physical and chemical agents, pass through the stomach unharmed, and that they are the infective agents. The vegetative, or motile forms, are found only in the feces in patients having symptoms of diarrhea or dysentery and these individuals are not infective to others unless cysts are present, as the motile forms cannot pass through the stomach. Accordingly, the patient having active dysenteric symptoms is not usually dangerous to others who come in contact with him, as his stool contains the motile form, which is not infective. He becomes dangerous, however, when his dysenteric symptoms disappear and the stools become formed, as it is then that the cysts begin to be found in his stool and these are the infective agents. The apparent anomaly then occurs of a convalescent, or symptomless patient, being dangerous to his associates as regards the transmission of his infection, whereas, during the acute stage of his infection, he was harmless to his associates in this respect. The so-called "healthy carriers" of this parasite, and those carriers whose symptoms are mild or atypical, are also generally infective to those about them, as their stools contain large numbers of cysts, and few, if any, motile forms unless diarrhea be present. From the standpoint of prophylaxis, it is most essential to remember that formed stools contain the cysts, or infective agents, while diarrheal or dysenteric stools are practically harmless, as they contain the motile, or vegetative forms. While this statement is true, it should be remembered that diarrheal stools produced by a cathartic are also dangerous, from the standpoint of transmission, as such stools contain both motile and encysted forms of the organism.

Entameba histolytica is normally a tissue parasite, living in the tissues composing the various coats of the human intestine, and infection with this parasite means in every instance injury to the mucous membrane of the intestine with the invasion of the underlying tissues by the organism. In addition, the parasite may be carried to other portions of the body through the blood stream or lymphatics where it may colonize and give rise to characteristic lesions. In the intestine the lesions produced vary all the way from a slight necrosis of the epithelial covering of the mucous membrane to the most extensive ulcerations involving all the coats of the intestine, while in the various viscera abscesses are formed, the most common and typical being the well-known amebic abscess of the liver.

The lesions are produced, as the writer has shown, by cytolytic and hemolytic substances present in the amebæ, for it is possible to extract such substances from cultures of this ameba with alcohol. In addition, the cytolysis of the tissues of the intestine results in the secondary invasion of the tissues with bacteria and these, if pathogenic, are thus able to

exercise their harmful action together with that of the parasite causing the primary lesion. *Entameba histolytica* thus brings about a real condition of "focal infection" in the intestine, for each lesion produced by this parasite, no matter how minute, unless it heals very promptly, becomes an area of potential focal infection with whatever harmful bacteria present in the intestine. The severity and character of the symptoms produced by the presence of the parasite in the intestine vary with the resistance of the individual and many individuals do not present any appreciable symptoms of the presence of the organism. However, it should be remembered that it is not necessary for definite symptoms of dysentery to be present in order that ulceration be present, for Musgrave and others have shown that extensive ulceration of the bowel may be present due to *Entameba histolytica* without there ever having been any evidence of dysentery noted, and in such cases the first evidence of the infection may be the occurrence of an abscess of the liver. The writer has observed several cases in which amebic abscess of the liver occurred in patients who gave no history of severe diarrheal or dysenteric attacks.

From this brief summary of the relation of *Entameba histolytica* to disease it is evident that the prophylaxis and treatment of these infections is of great importance. Their recognition depends upon the finding of the parasite in the feces of the infected individual, and this subject is fully discussed in many monographs devoted to protozoölogy and clinical diagnosis, and cannot be considered here. Suffice it to say, that the finding of the parasite in the feces is diagnostic and every individual in whom the parasite is found should be treated, even though no symptoms of the infection are present. Recently, the writer has devised a complement fixation test which has proven most useful in the diagnosis of infection with this parasite, using antigens prepared by extracting cultures of *Entameba histolytica*.

Resistance of Entameba Histolytica.—In order to intelligently employ prophylaxis it is essential that one know something regarding the resistance of the vegetative and cystic forms of *Entameba histolytica* to physical and chemical agents.

Vegetative Form or Trophozoïte.—As already stated, the vegetative, or motile, form of *Entameba histolytica* is destroyed by the gastric juice and cannot pass through the stomach of the human host without being killed. It is also very slightly resistant to physical agents, being quickly killed by extremes of temperature, and degenerating and disappearing from the feces within from one to four hours after their passage from the intestine. As these forms are only found in fluid or semifluid stools, except in comparatively rare instances, it follows that such stools are of little danger in transmission, as they do not contain cysts of the parasite, which, because of their resistance to the normal gastric juice and physical agents, are the transmitting agents of the infection. However, it should be remem-

bered that semifluid or fluid stools produced by catharsis will contain both vegetative and cystic forms of the parasite and are infective.

Cystic Form.—The cysts of *Entameba histolytica*, which are voided in immense numbers in the feces of individuals apparently in health (carriers), those presenting mild symptoms of infection, or those convalescent from acute or subacute attacks of dysentery, in all of whom the stools are formed or semiformed, are very resistant to physical and chemical agents, and this fact renders the prophylaxis of the infection exceedingly difficult. Since the cultivation of the parasite has been rendered possible a considerable amount of evidence has accumulated regarding the resistance of the cysts of *Entameba histolytica* to various physical and chemical agents and a brief summary of the more important data follows:

Thermal Death-Point.—Boeck, using washed cysts, obtained from the feces, determined that the thermal death-point was 68° C. (154° F.), but Yorke and Adams, using cultivation as a test of the viability of the cysts, found that the cysts did not excyst in cultures after exposure to 50° C. (122° F.) but that they withstood a temperature of 45° C. (113° F.) for thirty minutes.

Survival in Feces.—Thompson found that cysts remained alive in moist feces for a period of one month at room temperature but most of them died by the end of the third week. Yorke and Adams found that the cysts did not excyst in cultures, if removed from the feces by sedimentation and washing, for a period longer than ten days, but they did not ascertain the length of time the cysts remained alive in the feces at room temperature.

Survival in Water.—The length of time the cysts will remain viable in water depends largely upon the amount of contamination of the water with bacteria or other vegetable organisms, as molds. If feces are greatly diluted with water the cysts may remain alive for several weeks, according to Dobell and others. Boeck determined that if the cysts be removed from the feces by sedimentation and washing, and then placed in water, they will remain alive for about one month if there is little bacterial contamination, but if bacteria are very numerous the cysts will die within nine days. If kept in distilled water at temperatures varying between 12° and 22° C. (53° to 71° F.), the cysts will remain alive for as long as five months and if the preparations in distilled water be sealed the cysts will remain viable for seven months. Yorke and Adams found that washed cysts will develop into motile forms in cultures after being kept in ordinary water for seventeen days. It is thus evident that contaminated water may easily be the cause of infection under certain conditions although it is probable that in nature it is not as important in this respect as contaminated food.

Resistance to Desiccation.—The cysts of *Entameba histolytica* are very sensitive to drying and it has been found that they perish quickly un-

less kept moist. Wenyon and O'Connor, and others, state that drying kills them instantly. It is thus evident that this infection is not transmitted by dust as suggested by some observers.

Resistance to Various Chemicals.—It has already been stated that the motile forms, or trophozoïtes, are very sensitive to the gastric juice, being unable to exist in material containing a percentage of hydrochloric acid equal to that in the gastric juice. The cysts of *Entameba histolytica,* however, have been found to develop into motile forms in cultures after thirty minutes exposure to a 7.5 per cent solution of *hydrochloric acid;* that it required a 1 : 2500 solution of *mercuric bichlorid* and an exposure of thirty minutes to kill the cysts; and that 1 per cent solutions of *carbolic acid* and *lysol* required an exposure of thirty minutes in order to destroy these bodies. Several observers have also found that a 5 per cent solution of *formalin* killed the cysts in thirty minutes while a 1 per cent solution of *potassium permanganate* failed to do so after thirty minutes' exposure of the cysts to this agent. Wenyon and O'Connor found that a 1 : 250 solution of *cresol* killed the cysts in fifteen minutes while a 1 : 20 solution killed them instantly. Mills, Bartlett and Kessel found that the cysts remained alive in a 50 per cent solution of *alcohol* for one hour.

The effect of *chlorin* upon the cysts of this ameba is a question of great importance in prophylaxis as this agent is now so widely employed in the purification of water supplies. Wenyon and O'Connor showed conclusively that exposure for several hours in water containing chlorin in the proportion of 1 : 10,000 had no effect upon the cysts of *Entameba histolytica* and Yorke and Adams, using the cultural method of proving the viability of the cysts, found that it is necessary to add chlorin to water in a proportion of 1 : 10,000 in order to kill the cysts after thirty minutes' exposure, an amount of chlorin so large that it could not be used in water purification. Regarding their results they say: "The ordinary procedure of adding chlorinated lime or liquid chlorin to water in quantity sufficient to kill *Bacillus coli,* if present, is without effect upon *Entameba histolytica* cysts, and, in fact, the addition of this substance to water containing *Entameba histolytica* cysts is, for practical purposes, completely useless."

The observations of Wenyon and O'Connor, and Yorke and Adams have been confirmed in the Army Medical School laboratories by Captain St. John, and have also been confirmed by numerous other observers, so that it may be stated as a fact that it is impossible to render water safe, so far as the cysts of this parasite are concerned, by treatment, in any form, with chlorin, as the amount of the chemical necessary to kill the cysts is far in excess of the amount that can be used practically in water sterilization.

Survival in Flies.—Thompson and Thompson were the first to demonstrate that the cysts of *Entameba histolytica* could pass unharmed through the intestinal canal of flies and be voided in a viable condition in the drop-

pings of these insects, and their observations have been confirmed and extended by Wenyon and O'Connor, Roubaud, Root, and others. The cysts may remain in a living condition in the intestine of the common house fly for at least twenty-four hours and during all this time the feces of the insect may contain viable cysts. In some of the flies the cysts remain alive in the intestine for from thirty-six to forty-eight hours, and rarely more than two days. In flies drowned in water or milk, the cysts were recovered from the intestine in a living condition for as long as one week.

Application of Prophylactic Methods.—From what has been said of the resistance of the cysts of *Entameba histolytica* to various physical and chemical agents, it is evident that the prophylaxis of this infection is not as simple as would appear from our definite knowledge that infection must occur through the means of contaminated food or drink. Prophylaxis depends upon the protection of food and drink from the cysts of this parasite or the destruction of the cysts if they reach these objects. It is evident that food or drink may become contaminated by the cysts in many different ways, but the most common contamination results from the handling of food by carriers, the use of human excreta in the fertilization of garden truck, the droppings of flies and a contaminated water supply. It should always be remembered that the cysts of this parasite are the infective agents, and not the motile forms; as the cysts seldom, if ever, occur in patients having acute symptoms of dysentery, it follows that those suffering from acute amebic dysentery are not concerned in the transmission of the infection. Apparently healthy individuals who harbor the parasite, and those who are convalescent from attacks of amebic dysentery are the sources of infection, and such "carriers" are very numerous, especially in the tropics and subtropics. The vast majority of patients who recover from attacks of amebic dysentery become carriers of the parasite even though treatment has been apparently sufficient to rid them of their infection, and many individuals who have never suffered from dysenteric symptoms are carriers of *Entameba histolytica*. Prophylaxis of the infection, in order to be successful, should include the following procedures:

1. *The Detection and Treatment of Carriers.*—When one remembers that practically one of every eight or ten individuals in even the temperate zones harbors *Entameba histolytica* the difficulty of diagnosing and treating these infections becomes at once apparent. The majority of these individuals are carriers of the parasite and have no symptoms of the infection, although there are lesions present in the intestine caused by its presence, for at the present time there is no real evidence that this organism can multiply in the lumen of the bowel indefinitely without invading the tissues. The number of these carriers is so great that it is impossible to isolate and treat them, and the most that we can hope to accomplish is to recognize and render harmless those that have directly to do with the

preparation and handling of food. To this end, the feces of all food handlers should be very carefully examined and if *Entameba histolytica* is found, these individuals should be promptly removed from their occupation and properly treated. Such individuals should not be permitted to return to their occupation of food handling until the feces have been negative for this ameba upon three successive examinations, at least one week apart, and a feces examination of such individuals should be made at least once a month for a period of six months after the cessation of treatment. If such precautions cannot be taken, all food handlers who have been found positive for *Entameba histolytica* should be recorded and never again allowed to work in restaurants, mess halls, or kitchens, where they will handle food in any manner.

As it has been shown by many observers that, under ordinary conditions as regards treatment of amebic dysentery, most of the patients become carriers of the parasite, the proper treatment of the condition is of prime importance in the prophylaxis of amebiasis. Proper treatment will prevent patients from becoming carriers and thus will prevent the infection. The methods of treating amebiasis are detailed in the section of this contribution dealing with that subject, but it may be stated here that it is possible to rid most carriers of their infection without interfering with their daily duties.

2. *The Proper Disposal and Treatment of Feces.*—The proper disposal and treatment of human feces is of prime importance in the prophylaxis of amebiasis, for it is in the feces that the transmitting agents, the cysts, of *Entameba histolytica* are found. The best method of disposing of the feces is through properly constructed sewers emptying into the sea or other bodies of water that are not used as a source of human water supply, or into properly constructed sewage disposal plants. Where this method of disposal is not available the feces of carriers and of those convalescent from amebic dysentery should be disinfected before being disposed of, and this is best accomplished by mixing the stool with a solution containing one part of cresol to 200 parts of water, using enough of the solution to make the mixture distinctly fluid in consistence, and allowing it to stand for fifteen minutes before it is disposed of in any manner. While the danger of infection from the stools of patients suffering with acute symptoms of amebic dysentery is practically *nil,* it is the part of wisdom to disinfect such stools, also, in the manner prescribed. The use of other chemicals for stool disinfection in the case of cysts of *Entameba histolytica* should not be allowed as cresol is the only chemical which has been found efficient for this purpose.

3. *The Protection and Sterilization of Water Supplies.*—While it is probably true that the transmission of *Entameba histolytica* through a large, general water supply, as impounding reservoirs for large towns or cities, practically never occurs, it is true that small sources of water sup-

ply, as cisterns, small ponds, wells, springs and small streams, may become grossly contaminated with sewage containing cysts of this parasite, and become grave sources of infection. Therefore, the proper guarding of such sources of water supply from contamination with sewage is a prophylactic measure of great importance and one which should never be neglected. Where such precautions cannot be taken, or can only be partially successful, because of local conditions, the sterilization of the water is essential in prophylaxis. As the ordinary methods of sterilization of water by chlorination, or treatment with other chemicals, have been found of no value in destroying the cysts of this parasite, it will be necessary to resort to the boiling of all water used for domestic consumption. Boiling almost instantly destroys the cysts of *Entameba histolytica* and can be absolutely relied upon for the sterilization of water so far as this parasite is concerned.

4. *The Avoidance of Fresh Vegetables in Endemic Regions.*—In any locality where there is any suspicion that human excreta are used for the fertilization of vegetables, a common practice in many subtropical and tropical countries, the use of fresh vegetables should be avoided. Vegetables, fruits and all garden produce which may possibly come in contact with the feces when used in this manner should be forbidden, unless sterilized. Vegetable and fruit salads are especially dangerous because of the lettuce which they contain and which furnishes an almost ideal resting place for the cysts of *Entameba histolytica,* which may reach the leaves through this method of fertilization.

If it is desired to use fruits or vegetables which may have been fertilized in this manner, they may be rendered safe by thoroughly washing them in running water and then immersing them in boiling water for thirty seconds, the temperature of the water being kept as near the boiling point as possible. Vegetables like spinach, kale and lettuce should be separated leaf by leaf and each leaf immersed in boiling water. After being treated in this manner the fruits or vegetables may be freshened by placing in the ice box or by immersion in ice cold, boiled water.

5. *The Protection of Food from Flies.*—As it has been shown that the cysts of *Entameba histolytica* may remain in the intestine of flies unharmed for at least twenty-four hours, and be voided in the droppings of this insect, the protection of all food supplies from these insects is of great prophylactic value. It is not necessary to discuss the various means of protection that are available, but the most important are the use of screens for dining rooms or mess halls, flytraps and the "fly swatter."

6. *The Prevention of the Breeding of Flies.*—The prevention of the breeding of flies in regions where amebiasis is prevalent is an important prophylactic method for obvious reasons, and the well-known methods which have proven valuable in this direction should be adopted by the health authorities.

7. *The Education of the Public.*—The education of the public as regards the importance and method of transmission of amebiasis will be found to be a valuable prophylactic method. Individuals who are "carriers" of the parasite should be informed of the danger of their transmitting it to others and should be instructed regarding the measures that may be taken to prevent such transmission. The public should be informed as to the method of transmission of this parasite, its importance from a health standpoint, and the importance of the recognition and treatment of carriers, and the proper treatment of all individuals presenting symptoms of the infection. It should be recognized that amebiasis and amebic dysentery are strictly preventable conditions and that the well-known sanitary measures now employed in the prevention of typhoid fever, bacillary dysentery and cholera are equally efficient in the prevention of infection with *Entameba histolytica,* with the exception that chlorination of water cannot be relied upon, for all water that is suspicious must be boiled in order to render it harmless. Present knowledge regarding infection with this parasite demonstrates that in its epidemiological features it is comparable with the infections mentioned, and that the same general methods of prophylaxis are indicated, and, if properly enforced, will meet with the same measure of success.

TREATMENT OF AMEBIASIS

For convenience of description the treatment of amebiasis may be divided into the treatment of carriers of the infection and the treatment of acute amebic dysentery.

Treatment of Carriers of Entameba Histolytica.—By the term "carriers" are understood those individuals who harbor *Entameba histolytica* but who have either no symptoms of the infection or in whom the symptoms are so mild or atypical that the individual has not considered medical attention necessary. In reality, the latter type of individual is not a carrier in the strict sense of the word but is actually suffering from symptoms of infection with the parasite. However, in considering the treatment of amebiasis, it is convenient to classify these mild infections with those that do not show symptoms, for it has been found in practice that the treatment of the carrier and those showing mild and atypical symptoms is the same, while that of individuals presenting severe symptoms, or those having amebic dysentery, differs in important particulars.

In the treatment of carriers and those presenting mild or atypical symptoms of infection, the writer has found that the most successful drug available is acetarsone (stovarsol). Acetarsone, or acetylaminohydroxyphenylarsonic acid, is a synthetic arsenical preparation containing from 27.1 to 27.4 per cent arsenic. It was introduced by the French for the treatment of syphilis, and has the advantage of administration by the mouth instead of intravenously, as in the case of the arsphenamins. While

not as efficient in the treatment of syphilis as the latter drugs, it has been extensively used in the treatment of amebic dysentery and the writer has found it of very great value in ridding carriers of *Entameba histolytica*. The drug can be administered to carriers and those having mild symptoms of infection without interfering with the occupation of the patient, whereas, in the case of other drugs used for this purpose, the patient must be in bed in order to secure the best results. The drug is supplied in tablets each containing 0.25 gram and each tablet is marked in such a way that it can be accurately broken in halves if it is desired to administer less than one tablet at a dose.

In the treatment of individuals presenting no symptoms of the infection, *i.e.*, so-called "healthy carriers," the following method is recommended: One-half a tablet is given by mouth three times a day for one week, the treatment discontinued for a week, and the same amount of the drug administered for another week in the same manner. This dosage has been found sufficient and is not attended, in our experience, with any unpleasant symptoms due to the drug.

In those individuals in whom symptoms suggestive of infection with *Entameba histolytica* are present, as repeated attacks of diarrhea with alternating periods of constipation, digestive disturbances of various kinds, pain and discomfort in the abdomen, and the nervous symptoms which accompany such symptoms, it is best to give a larger dose of the drug. The writer has found that in such cases one tablet three times a day, with a week's cessation of treatment, and the same dose for another week, is most efficient in causing the permanent disappearance of the parasite.

It should be remembered that acetarsone is a very powerful arsenical preparation and that symptoms of arsenic intolerance sometimes arise during its administration. These symptoms consist in colicky pains in the abdomen, a profuse diarrhea, puffiness of the eyelids, and erythematous eruptions, bilateral in character, and most often noted upon the forearms and wrists, while a peripheral neuritis has been described by some writers. A rise in temperature is sometimes observed. These symptoms are seldom serious and quickly disappear if the drug is stopped. If it is necessary to stop the drug, because of such symptoms, it should be resumed in smaller doses after the symptoms disappear, and the administration carefully checked and stopped immediately upon the reappearance of any symptoms of arsenical intolerance.

The treatment outlined above has been extensively used by the writer in the class of infections with *Entameba histolytica* in which it is recommended, and the results have been most satisfactory. One course of treatment in the instance of carriers with no symptoms has resulted in most cases in causing the disappearance of the organism from the feces and relapses have not occurred at the end of six months after cessation of treatment in the individuals checked for that length of time. In the

instance of cases presenting very mild or atypical symptoms a second course of treatment has been necessary in a few instances, but the second course was invariably followed by the disappearance of the parasites.

In all of the individuals presenting symptoms of the infection, the symptoms disappeared, and a gain in weight and in a general feeling of well-being was noticeable in every instance. In the patients in whom the blood-serum was positive, when tested with the complement fixation test recently devised by the writer, the reaction became negative in from one week to seven weeks after the cessation of treatment, so that it is believed that this method of treatment is specific in the class of cases for which it is recommended, *i.e.,* apparently healthy carriers of the infection and those presenting mild and atypical symptoms of infection, not sufficient to demand medical attention under ordinary circumstances.

Several authorities have recommended the use of emetin hydrochlorid, or chiniofon (yatren), in the treatment of carriers and those with mild infections with *Entameba histolytica* and, undoubtedly, both of these drugs are useful in this respect, but they are both more toxic than acetarsone and are not administered as easily, as emetin hydrochlorid should be given hypodermically and chiniofon should be administered both by mouth and by rectal injections. As acetarsone gives such excellent results in the treatment of this class of cases and is so readily administered, without interfering with the occupation of the individual, it is believed that it should be the remedy of choice in the treatment of this type of amebiasis.

Treatment of Acute and Chronic Amebic Dysentery.—The treatment of amebic dysentery has always been a most interesting subject to the practitioner who is called upon to treat this condition, and, in the light of our present knowledge of amebiasis, should be of interest to physicians in all parts of the world, for the impression that amebic dysentery is confined to the tropics and subtropics has long since been exploded and we know now that it is prevalent, although to a much lesser extent, in the temperate zones throughout the world. It is probable that amebic dysentery is much more prevalent than is now believed in temperate regions, and it is surely true that acute and chronic diarrheal attacks are much more frequently caused by *Entameba histolytica* than is generally believed. It is now well established that amebiasis is a very common condition in all parts of the world and that in all parts of the world it is often accompanied by acute and chronic diarrhea, and much less frequently by the symptoms we know as typical of amebic dysentery. The latter symptoms are frequently noted in the tropics, while the former are even more frequently observed in temperate regions, but are seldom recognized as being due to this parasite. These facts render the treatment of amebiasis of intense interest to all physicians, for the recognition and proper treatment of this condition will prevent the development of that dreaded complication of amebiasis, abscess of the liver. The writer has

observed several instances of amebic abscess of the liver occurring in individuals who had suffered from recurring attacks of diarrhea for months, or even years, but in whom the true nature of the condition was not suspected, and the amebic infection remained unrecognized until the abscess developed. In other instances, the writer has observed an abscess of the liver develop in individuals in whom no history of diarrhea or dysentery could be elicited, *i.e.,* in apparently healthy carriers of the parasite, so that it is obvious that such infections should be recognized and properly treated.

There have been numerous so-called "specific" treatments evolved and recommended in the treatment of amebic dysentery but most of them have been found unsatisfactory and inefficient. To-day, it may be said that emetin hydrochlorid, emetin bismuth iodid, bismuth, chiniofon (yatren) and acetarsone (stovarsol) are the only remedies that enjoy the confidence of the medical profession and each of these has its enthusiastic advocates. The choice is largely one of individual experience but it is believed that, so far as permanent cure of the amebic infection is concerned, emetin hydrochlorid and emetin bismuth iodid, as well as bismuth in any form, are less efficient than chiniofon or acetarsone. However, it is sometimes advantageous to combine certain of these remedies in the treatment of the condition, and when this is done, better results are often obtained than by using one remedy alone.

For convenience of description the method of using each of these drugs in the treatment of amebic dysentery will be considered separately.

Emetin Hydrochlorid.—The amebicidal properties of emetin were first demonstrated by Lieutenant Colonel E. B. Vedder, of the United States Army Medical Corps, in the instance of free-living amebæ in cultures, and as a result of his observations, Leonard Rogers first tried the drug in the treatment of amebic dysentery. The immediate results were so striking that emetin hydrochlorid soon became the standard drug used in the treatment of this condition and was, for many years, considered the only specific drug for *Entameba histolytica* known to medical science. Its effect in causing the rapid disappearance of the acute symptoms of the infection is most striking and the patient is usually well on the road to a symptomatic recovery within a few days after the beginning of treatment with this remedy. But it was soon found that many of the patients so treated relapsed, and continued observation has shown that a cure of amebic infection is seldom accomplished by emetin hydrochlorid alone, even though administered over long periods of time and in doses that endanger the health of the patient. Continued experience has shown that emetin hydrochlorid is of comparative little use in chronic amebic dysentery but finds its greatest field of usefulness in the treatment of the initial acute attack, where its power in causing the rapid disappearance of symptoms in most cases makes it a remedy of great value in the treat-

ment of this type of amebiasis. It is not as valuable a remedy as emetin bismuth iodid, and should not be used if the latter drug is available.

Emetin hydrochlorid has been administered orally, subcutaneously, intramuscularly and intravenously. It is best given orally if it can be retained in sufficient dosage to be efficient, but subcutaneous administration is favored by many practitioners. It should not be administered intramuscularly or intravenously. Combined administration by mouth and subcutaneously is often resorted to in stubborn infections and has been found more efficient than by either method alone.

When given by mouth emetin is administered in the form of pills or capsules coated with keratin, salol or some substance more or less insoluble in the gastric juice, and when given in this form the drug is much less nauseating in its action than when administered in ordinary tablets or powder form. The whole powdered root of ipecac is sometimes used instead of emetin hydrochlorid, but is much more emetic in its action and should not be used if emetin can be obtained. When given by mouth the dose of emetin hydrochlorid should not exceed 1.5 grain (0.09 gram) per day, best given in equally divided doses morning and evening. However, it is seldom that emetin hydrochlorid is given alone by the mouth, the most efficient treatment being by mouth and subcutaneously. When thus administered, ½ grain (0.03 gram) of the drug is given by mouth every night and 1 grain (0.06 gram) subcutaneously, every morning, for twelve consecutive days. Great care should be used that asepsis is secured during the hypodermic injection and it is useless to administer less than the amount of emetin noted if one expects good results so far as a *cure* of the infection is concerned. Even with this combined treatment not over 25 to 30 per cent of the cases are cured, and the writer is very doubtful if this treatment really cures more than 10 to 15 per cent. It is a most efficient treatment in controlling the acute dysenteric symptoms but rarely results in cure of the infection. If a relapse of the symptoms occurs, or the parasites are found again in the feces, the course of treatment may be repeated but experience has shown that comparatively few cases of amebiasis are cured with emetin hydrochlorid alone. The patient must be kept at rest in bed during the entire course of treatment.

Emetin hydrochlorid is a toxic drug and the patient must be carefully watched during its administration by the physician for the possible appearance of toxic symptoms. When given over too long a period of time, or in too large a dose, emetin causes severe diarrhea, often dysentery, myocarditis, neuritis, great muscular weakness, and physical and nervous prostration; even collapse and sudden death may follow these symptoms, or occur suddenly during the administration of the drug, and before marked symptoms of poisoning have been noted. The writer has observed deaths following the administration of emetin hydrochlorid and

many cases in which profound muscular and nervous depression followed the continuous administration of the drug. For this reason, the writer believes that the use of emetin hydrochlorid in the treatment of amebiasis should be confined to the treatment of the acute dysenteric stage of the infection, if it is used at all, and that repeated courses of treatment with this drug should never be countenanced if other efficient remedies are available.

Emetin Bismuth Iodid.—This preparation, the double iodid of emetin and bismuth, is generally considered as more efficient in the treatment of amebiasis than is emetin hydrochlorid, and is often combined with the former, emetin hydrochlorid being administered subcutaneously and the double iodid by mouth. With this drug, as with emetin hydrochlorid, the patient must be kept in bed during the treatment, for rest is essential in order to prevent or lessen nausea and to lessen liability to heart failure. If the dysenteric symptoms are very severe a hypodermic of 1 grain (0.06 gram) of emetin hydrochlorid should be given and repeated in twenty-four to thirty hours, if necessary, and then the treatment with emetin bismuth iodid commenced as soon as possible. When once started the treatment should be persisted in until the amount of the drug recommended has been taken, for interrupting the treatment, or shortening it, invariably results in failure to cure the infection and a clinical relapse occurs sooner or later.

The dose of emetin bismuth iodid is 3 grains (0.2 gram) daily for twelve consecutive days. It is given at night after a meal, with a cup of hot tea or broth, the patient lying flat in the bed without pillows. Nausea generally occurs during the first or second night, salivation is present, and vomiting may occur on the first night but seldom upon the second night or thereafter, although nausea may occur at intervals throughout the course of treatment and there may be slight attacks of vomiting. After from four to six days, or later, diarrhea usually occurs, but this should not cause any anxiety and, unless excessive, requires no treatment. Many authorities advise the reduction or cessation of the drug if diarrhea occurs but the treatment should be persisted in unless the diarrhea is very excessive and accompanied by symptoms of exhaustion or evidence of a weak heart action. Like emetin, this drug is a toxic substance and sometimes it is necessary to stop the treatment because of a failing pulse or extreme muscular or nervous prostration. At the termination of the treatment the patient is usually mentally depressed and there may be considerable muscular weakness but a reaction occurs promptly upon cessation of the treatment and in a few days convalescence is complete. Precautions should be taken that the patient does not overexert during the first two or three weeks after cessation of the treatment and it is best to keep him in bed for two or three days after completion of the treatment. The pulse should be carefully watched throughout the treatment and the drug stopped if

there is marked reduction in its frequency and strength, or if it becomes irregular in its rhythm.

Chiniofon (Yatren or Yatren 105).—This drug, first introduced by the Germans in the treatment of amebic dysentery, is a synthetic preparation, chemically, iodin oxyquinolin sulphonic acid, a combination in which the iodin is probably the chief amebicidal agent. This preparation is a powerful intestinal disinfectant and can be administered orally, hypodermically or by rectal injections. In practice it is usually given by the mouth and by enemata, although it may be administered either subcutaneously or intravenously. The course of treatment usually recommended for an adult is 15 grains (1 gram) in powder form in cachets, capsules or keratin coated pills, three times a day, for ten days, and proportionate doses for children. After an interval of one week to ten days the course of treatment should be repeated. Most authorities prefer to use the drug in conjunction with emetin, the latter drug first being used to control the symptoms and chiniofon then substituted.

To secure the best results with this drug it should be given by the mouth and by enema simultaneously, and it has been found that the dose of 15 grains (1 gram) three times a day usually causes severe diarrhea, so that this dose has been reduced to one-half that amount by most observers. The following method of treatment with chiniofon has been found very satisfactory in our hands and results in the disappearance of the amebæ and a permanent cure in a large proportion of the individuals so treated.

The patient is given 8 grains (0.5 gram) of chiniofon by mouth, either in cachet or keratin coated pills, three times a day for ten days. At the same time a daily enema is administered of 200 c.c. of a 2.5 per cent solution of chiniofon in distilled water or normal salt solution, which is retained for as long as possible. With practice this enema may be retained for several hours and the longer it is retained the more efficient will be the treatment. During the treatment the patient must be confined to bed and upon a carefully restricted diet of semiliquid character, but a more liberal diet may be allowed if the drug does not produce diarrhea. Many authorities prefer to use the full dose of the drug (15 grains) and stop its administration if severe diarrhea appears, but it is believed that better and more permanent results are obtained with the dosage recommended above. Toxic symptoms have not been observed with the smaller dosage and it is almost invariably possible to complete the entire treatment covering ten days.

Patients who have completed a course of treatment with chiniofon should have their feces examined at intervals for at least three months, in order to ascertain if the amebæ has reappeared, and, if so, the treatment should be repeated. The relative efficiency of treatment with emetin bismuth iodin and with chiniofon is largely a matter of opinion, but it

is believed that the consensus of opinion at present is that chiniofon is more efficient in causing the permanent disappearance of the amebæ and a cure of the infection. It appears to have, also, the advantage of being a much less toxic drug than emetin bismuth iodid and to be especially useful in long-continued infections in which emetin or emetin bismuth iodid have failed to eradicate the parasites. Absorption of the drug can be easily demonstrated by testing the urine with perchlorid of iron, as chiniofon is excreted in the urine and gives a green color when the urine is tested with this reagent.

Acetarsone (Stovarsol).—This drug has also been largely used in the treatment of acute and chronic amebic dysentery and has proven itself by excellent results. The method of administration is the same as when given in the treatment of carriers, which has already been described, but the full dose of 4 grains (0.25 gram) three times a day in tablet form should be given, unless symptoms of arsenic intoxication appear, when the drug should be discontinued. This dose should be administered for one week, a week without treatment allowed to elapse, and the drug repeated, in the same dosage, for one week. If the dysenteric symptoms are acute, it is best to control these with emetin and then commence the treatment with acetarsone. In the acute exacerbations of the chronic infections the same treatment should be followed, but in the intervals between acute attacks, acetarsone should be administered alone.

While the results of treatment with acetarsone do not appear to be as striking in the treatment of acute amebic dysentery as in the treatment of "carriers," it appears from the evidence that has accumulated that this drug is a very valuable one in the treatment of this form of dysentery, and is especially valuable in those chronic infections which have resisted treatment with emetin hydrochlorid or emetin bismuth iodid. In the writer's opinion this drug should be given a thorough trial in every case of acute and chronic amebic dysentery before resorting to the use of the other remedies mentioned, both because of its simplicity of administration, and its proven efficiency in the treatment of carriers and those individuals presenting mild symptoms of infection with *Entameba histolytica*. Toxic symptoms due to the drug should be carefully watched for and the drug discontinued as soon as the symptoms appear.

Bismuth.—In the form of the subnitrate or the subcarbonate, bismuth has enjoyed considerable popularity in the treatment of amebic dysentery and this method of treatment is especially recommended by Deeks and James, who have had a wide experience with this condition in the Canal Zone and Panama. In his latest communication, James recommends the prolonged use of subnitrate of bismuth, in doses of from 12 to 14 grams, three times a day, combined with rest, irrigation of the intestine when needed, and a proper diet, and states that with this treatment satisfactory results will follow in a large proportion of the cases. He uses emetin in

conjunction with this treatment in doses that the patient can tolerate. The writer has had no experience with the combined treatment with emetin and bismuth subnitrate, but has observed scores of acute and chronic amebic dysentery cases treated with bismuth subnitrate alone, and has yet to see a single case that has been cured by this drug, even when used in enormous doses.

Many other remedies have been advocated in the treatment of amebic infection, but none has stood the test of time and experience. The arsphenamins, mercurochrome, "kurchee" bark, "Kho-sam," chaparro amargosa and simaruba have all been used extensively in the treatment of this condition and none of them have proven of real value in curing the infection. Symptomatic improvement often follows the use of these remedies but permanent disappearance of the amebæ causing the symptoms does not follow.

Treatment of Amebic Hepatitis.—It appears to be the opinion of all who have had a large experience in the treatment of the hepatitis that frequently occurs as a complication of amebic infection, that emetin hydrochlorid, or emetin bismuth iodid, are especially valuable in this condition, being much more efficient in overcoming the infection in the liver than in the intestine. The drugs are administered in the same manner as in amebic dysentery and the same precautions should be taken as regards toxicity. The hepatitis quickly disappears after the administration of emetin and it has been claimed that this drug is capable of causing the healing or absorption of small liver-abscesses caused by the parasite. If large abscesses are present they should be drained or aspirated and emetin administered.

General Treatment.—Patients suffering from acute amebic dysentery, or an acute exacerbation of a chronic amebic infection, should be confined to bed and not allowed to leave the bed for any purposes while the symptoms are acute. Complete rest is a very valuable part of any treatment of the acute symptoms, and the best results will be secured if patients are strictly confined to their bed during treatment and for two or three days after the treatment has been stopped.

Diet is of very great importance during the acute symptoms of the infection and the smaller the amount of food taken, the better, as long as the strength of the patient is conserved. During the acute symptoms the diet should be liquid in character, consisting of broths, especially chicken broth, barley water, egg albumin, and milk with lime water after the acute symptoms have begun to subside as the result of treatment. Pure milk or malted milk may be used when the symptoms have improved and as improvement continues, eggs, either soft boiled or mixed with milk, soft puddings, and a semifluid diet should be the rule. A full diet should not be resumed until all symptoms have disappeared and the stools are formed, and even then great care should be taken to avoid foods that are

known to irritate the intestine or to disagree with the patient. Smoking should not be allowed during the treatment and alcohol should be absolutely forbidden.

During convalescence chilling should be especially avoided and it should be remembered that, although the amebic infection may have been eradicated, attacks of mild, or even severe, diarrhea are frequently observed in patients who have recovered from amebic dysentery. The frequency and severity of these attacks will vary, of course, with the amount of damage done by the amebæ to the mucous membrane of the intestine, and also according to care taken to avoid articles of food that irritate the bowel.

A special warning is needed regarding the use of alcoholic stimulants by individuals suffering from amebiasis. There is no more common cause of a relapse in long standing cases of amebiasis than the use of alcoholic drinks, and many severe acute exacerbations of chronic amebic dysentery occur as the result of a drinking bout or the indulgence in alcoholics at dinner parties or elsewhere. Individuals who are infected with *Entameba histolytica* should never indulge in alcoholics, for attacks of severe diarrhea often follow such indulgence in carriers who otherwise present no symptoms, and, as has been stated, alcoholic stimulants are often the cause of acute dysenteric attacks in patients suffering from subacute or chronic amebic dysentery.

Test of Cure.—The only criterion of value as to the actual cure in a case of amebiasis is the permanent disappearance of the amebæ from the feces. It should be remembered that acute symptoms often disappear spontaneously and that their disappearance after any of the methods of treatment recommended is almost universal, but, as in malarial infections, this does not always mean that the patient is cured. Every treated case of amebiasis should have repeated examinations of stools made for a period of at least three months, and better, six months, after the cessation of the treatment, and if the amebæ reappear, the treatment should be repeated. Too often a patient is discharged as cured after the subsidence of the symptoms, only to relapse later and to become a sufferer from the chronic type of amebic dysentery.

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CHAPTER XXIV

GRANULOMA INGUINALE AND LYMPHOGRANULOMATOSIS INGUINALIS

John A. Hillsman and H. M. Zimmerman

GRANULOMA INGUINALE

The chief manifestation of this disease is a chronic ulcerating and granulating lesion of the skin, occurring most frequently, but not exclusively, in the genital region. It is most commonly encountered in tropical countries, but is definitely known to be endemic throughout the world.

Etiology.—Donovan, in 1905, first described a pleomorphic intracellular organism which he considered the causative agent of this disease. These organisms can be grown in Sabouraud's media, and when stained with Wright's or Giemsa's stain appear as oval, pink structures containing blue bacillary or diplococcoid bodies in their longitudinal axis. In smears from the skin lesion these organisms are found in the cytoplasm of large mononuclear cells. There is agreement among most writers that these "Donovan bodies" are the etiological agent of granuloma inguinale. And yet, because of the failure to reproduce the disease in animals from pure cultures of these bodies, other etiological agents have been suggested by some authors, among whom may be mentioned Goldzieher and Peck who have isolated a pleomorphic organism which they believe is the causative agent.

Pathology.—Since it is not definitely established that the disease is of venereal origin the incubation period is unknown. The experimental work of McIntosh with tissue transplants, however, would indicate that the incubation period is from two to four weeks. The lesion begins as a vesicle or papule which goes on to the formation of a pustule that ruptures and exudes a small amount of purulent material. The primary lesion is painless, and the regional lymph-nodes are uninvolved until secondary infection occurs. The pustule spreads concentrically, at the same time showing a tendency towards central healing. The disease is auto-inoculable, and other areas of ulceration and granulation in the vicinity of the original lesion usually develop. As the result of secondary infection fistulæ to the surrounding organs are not uncommon. The well-developed skin lesion is that of exuberant granulation tissue, soft and red, overlapping the surrounding healthy skin edges. A scanty, mucoid exudate of inoffensive but

characteristic odor covers the base. Histologically the lesion is not characteristic. Both hyperkeratosis and extensive granulation tissue are present. The exudate is the usual one associated with chronic and acute infection. Donovan bodies are usually found in the mononuclear cells.

Diagnosis.—A diagnosis is made of this condition when there is present a skin lesion marked by extensive granulation tissue, characteristic odor, painless nature, presence of Donovan bodies, favorable response to antimony therapy, and failure to involve regional lymph-nodes. This disease is differentiated from other lesions that may occur around the genitalia, such as, condylomata, chancre, chancroid, tuberculosis, epithelioma, sarcoma and lymphogranulomatosis inguinalis, as follows: The characteristic wartlike excrescences of condylomata, the presence of the *Spirochæta pallida* and of a positive blood Wassermann in syphilitic infections, the finding of the Ducrey bacillus in chancroid, the characteristic histological picture and the guinea-pig inoculation in tuberculous lesions, and the characteristic histological pictures of epithelioma and sarcoma. The differential diagnosis of granuloma inguinale and lymphogranulomatosis inguinalis is discussed under the latter condition.

Fig. 1.—Drawing of the Ulcerating and Granulating Skin Lesion of Granuloma Inguinale in the Genital Region of a Colored Female.

Treatment.—Tartar emetic is considered specific in the treatment of this disease. The drug was first described as being used successfully in the treatment of granuloma inguinale by Arazao and Vianna, in 1913. Antimony potassium tartrate 0.1 gram dissolved in 10 c.c. of isotonic salt solution is sterilized, and is given intravenously. This dose is repeated at weekly intervals in ambulant cases and every other day in hospital cases. Relapses are frequent after incomplete treatment and ten intravenous treatments should be given after the lesion is completely healed. The disadvantage of tartar emetic is that it is extremely irritating to the body tissues and can not be administered subcutaneously or intramuscularly. When given intravenously it tends to obliterate the veins and for this reason injection should be started in

the most distal parts of the veins. Tartar emetic is also highly toxic, and ordinary dosages, especially when given too rapidly, may cause headaches, dizziness, nausea and vomiting. High dosages sometimes produce rheumatoid pains of a severe character, and deaths have been reported from antimony poisoning.

The use of sodium antimony thioglycollate and of the triamid of antimony thioglycollic acid in the treatment of granuloma inguinale was first described by Randall. The compounds have the same therapeutic effect upon the disease as tartar emetic, but have the advantages of being less
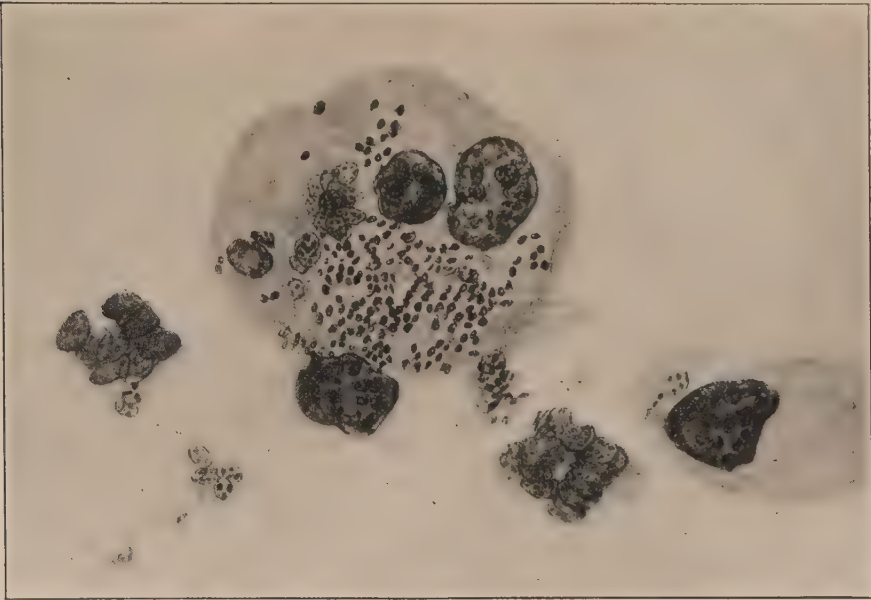
FIG. 2.—OIL IMMERSION. GIEMSA'S STAIN.

Drawing of a microscopic preparation from the skin lesion of granuloma inguinale, showing the extra- and intra-cellular Donovan bodies.

toxic and less irritating to the body tissues. Of the two compounds, sodium antimony thioglycollate is the least toxic and irritating. It also has the highest antimony content and is given in dosages of 40 to 80 milligrams intravenously, dissolved in isotonic saline, and sterilized.

X-ray therapy was used quite extensively in the treatment of granuloma inguinale when the lesion was thought to be tuberculous in nature. At the present time radiation is believed to be of value only in the intractable cases, and then must be used in conjunction with antimony therapy. The X-ray dosage is usually from two to sixteen exposures, 5 inches, 4 milliamperes, spark gap 14 centimeters, filtration 0.5 to 1 millimeter of aluminum. Radiation is supposed in these cases to break down the sclerosing tissue of the lesion, which theoretically blocks the antimony com-

pounds from acting on the etiological agent. X-ray should certainly be tried in obstinate lesions in conjunction with the antimony therapy.

Local treatment is only that of cleanliness. Surgical procedures are useless. Irrigation with hydrogen peroxid, or potassium permanganate, 1 : 5000, will keep the lesion clean and at the same time act as a deodorant.

LYMPHOGRANULOMATOSIS INGUINALIS

Lymphogranulomatosis inguinalis, sometimes called "climatic bubo" or "strumous buboes of the groin," is a contagious venereal disease of unknown etiology, transmitted by sexual intercourse. The initial lesion appears on the glans penis or the prepuce in the male, or on the vulva in the female as a small indurated, non-tender, herpetiform lesion with a slight serous discharge. This lesion is said to be absent in some cases. The incubation period following coitus is from one to six weeks. Following this, there is a period of quiescence in which the painless genital sore is the only manifestation. In several weeks the inguinal nodes on one side, more rarely on both sides, become enlarged, indurated and painful. At first they remain discrete, but soon a periadenitis develops, the nodes become matted and the overlying skin becomes involved, appearing bluish-red and indurated. Fluctuating areas develop which on aspiration yield yellow, purulent fluid. The picture is now one of inguinal adenitis which has gone on to suppuration. The iliac nodes become enlarged and tender in over half of the cases reported, but suppuration, on the contrary, does not occur. The

Fig. 3.—Photograph of the Skin Lesion of Lymphogranulomatosis in the Inguinal Region of a White Male.

skin over the mass breaks down, and with the relief of tension, pain and tenderness subside. A chronic, ulcerating, secondary infected area develops with numerous sinuses in the skin. Healing is extremely slow, and sometimes no change is noted for many months.

Constitutionally, there are no symptoms during the period of incu-

bation and the initial lesion, but during the stage of suppuration, before rupture or the institution of drainage, there may be symptoms suggestive of septicemia, such as high temperature, delirium and stupor. The blood-picture varies; in some cases there is a marked increase in the leukocytes, in others a normal count and in still others leukopenia. There is usually slight anemia.

Etiology.—The specific bacteriology of this disease is unknown. Sub-cutaneous, intramuscular, intraperitoneal, intratesticular and intracere-bral injections of the purulent material from the involved inguinal lymph-nodes and of diseased lymph-node particles have yielded negative results for the most part. Gamna, DeBella and Virgillo alone have been successful in producing lymph-node involvement in experimental animals, but there is no uniformity of opinion as to the etiologic agent, pseudodiphtheria and streptothrix-like organisms, *Micrococcus paramelitensis* and various amebæ having been mentioned in this category.

Pathology.—The histologic picture of the enlarged, indurated inguinal nodes shows diffuse granulation tissue infiltrated with numerous plasma-cells, small stellate and branching abscesses rich in endothelial-like cells and containing also an occasional giant-cell, and small particles (so-called Gamna bodies) in the cytoplasm of large mononuclear cells. The skin in-volvement which follows the suppuration of the inguinal lymph-nodes is one of chronic ulceration, infection and granulation tissue formation. Superficial sinuses in the skin radiate out from the central ulcerated area towards the healthy skin on the periphery. The formation of granulation tissue is not nearly as extensive as in granuloma inguinale. Histologically the skin lesion is merely that of a chronic infectious process with ulcer-ation.

Diagnosis.—A history of sexual intercourse followed in from one to six weeks by an enlargement and induration of the inguinal lymph-nodes which become quite painful and suppurate if not removed, with secondary involvement of the skin, together with negative bacteriological findings, strongly suggest the diagnosis. The chronicity of the course once the skin is involved and the refractility to treatment support this diagnosis.

Recently Frei and Hoffmann reported a skin test for this disease which gave a typical reaction in twenty of twenty-four cases clinically diagnosed as lymphogranulomatosis inguinalis. Their method is to remove by needle puncture a small quantity of the purulent material from the involved inguinal nodes, dilute this from five to ten times with a sodium chlorid solution, then heat for two hours at 60° C. the first day and for one hour the second day, and to inject intracutaneously 0.1 c.c. of the diluent. In persons suffering from the disease, a strong inflammatory reaction ensues, which continues to the formation of a papule. In none of the controls was a positive skin test obtained. It is noteworthy, however, that a number of

the patients with lymphogranulomatosis reacted positively with vaccines prepared from a variety of known organisms, such as *Bacillus coli, Bacillus pseudodiphtheriæ,* etc.

This disease is so frequently confused with granuloma inguinale, more so than with any other condition of the genital region, that the following points are offered in their differential diagnosis:

1. Granuloma inguinale is primarily a disease of the skin; lymphogranulomatosis inguinalis first involves the lymph-nodes and only secondarily the skin.

2. Donovan bodies can be demonstrated in the majority of cases of granuloma inguinale; these bodies are not found in lymphogranulomatosis inguinalis.

3. Patients with granuloma inguinale usually respond quite favorably to treatment with tartar emetic; lymphogranulomatosis inguinalis is notoriously refractive to any therapy.

4. According to Frei and Hoffmann their intradermal test is specific for lymphogranulomatosis inguinalis.

Treatment.—An early diagnosis of the condition, before the suppurating inguinal lymph-nodes have produced ulceration of the overlying skin with secondary infection, and the prompt excision of these nodes offer the best chances for an early cure. Once the skin has become infected and ulcerated the condition is slowly progressing and notoriously refractive to treatment. Local cleansing with antiseptic solutions is but a palliative measure. Tartar emetic, as well as other types of intravenous therapy, and X-ray and radium treatments all fail to influence this condition favorably. Where possible, excision of the skin lesion with a wide margin of healthy surrounding skin should be attempted. The only contra-indication to this surgical procedure is a lesion of such great extent that a complete removal would result in serious circulatory disturbances from the resulting scar tissue. Emetin hydrochlorid has been suggested, but apparently this drug has little effect upon the lesion. This ulcerating lesion, apparently unaffected by any therapy, usually goes on to spontaneous healing in a period of from two to four years.

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CHAPTER XXV

RADIOTHERAPY IN THE TREATMENT OF DISEASED TONSILS

Laura A. Lane

The medical literature pertaining to the tonsil, its pathology and treatment by various surgical operations or other procedures is enormous. The very fact that this literature is so voluminous, shows that we have not yet arrived at a satisfactory method of treating all types of pathologic tonsils.

As far back as 1905, Heineke reported that lymphoid tissue is very susceptible to the Roentgen ray. Many others have confirmed his observations. The tonsil is largely composed of lymphoid tissue and is, therefore, susceptible to radiation therapy. Roentgen ray therapy was used in the treatment of cervical adenitis many years before it was reported as useful in the treatment of pathologic tonsils. Van Allen reviewed a series of cases of tuberculous adenitis, many being treated twelve years previously. He found the majority showed no tonsil symptoms although all had done so before the raying. Price also investigated fifty cases of cervical adenitis with tonsillitis and found that 80 per cent had never had an attack since the gland radiation treatment.

It was not, however, until 1920 that Portmann called attention to the value of radiotherapy in tonsillitis as compared with surgery. Portmann says Regaud and Nogier presented the results of treatment of six cases of diseased tonsils to the medical and hospital society of Lyons in 1913. Portmann adds that with the newer technic his results have been better than theirs and he considers it the treatment of choice in subacute tonsillitis and in cervical adenitis. In addition to the types described by Portmann, we may add that radium in several cases of severe acute follicular tonsillitis gave very prompt relief.

The following year Witherbee and his coworkers at the Rockefeller Institute reported favorably on a series of patients with hypertrophied tonsils and adenoids, treated by the Roentgen ray. The writer had done some three thousand tonsillectomies, some of the patients being observed afterward over a period of many years. Only about half were relieved of their frequent colds, sore throats, ear and other complications for which they had sought advice. A survey of more than 100 patients having tonsillectomies performed by skilled operators in a large out-service department of a general hospital showed similar results. A review of more than

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30,000 tonsil cases showed much the same after-results. Such evidence seemed a bit discouraging and seven years ago we began the use of radiotherapy in carefully selected cases. The results, in those who took sufficient treatments, in many instances have been good and compare favorably with a group of operated cases. Early it was seen that radium was the preferable agent due to the fact that it could be applied wherever needed. A testimony to the efficiency of radium is seen in the many physicians who have had it used in their own tonsils, also in those of members of their families, and who refer their patients for radium treatment.

Radiotherapy is not to be used promiscuously on all types of tonsils. There are certain very definite indications and contra-indications to its use as follows:

Types of tonsils best suited to radiotherapy:

1. Soft, hypertrophied tonsils with little redness of the mucous membrane or the pillars.
2. Tonsils with some redness and secretion in the crypts, but clinically giving no signs of systemic infection.
3. Certain early cases of catarrhal deafness due to large tonsils and considerable lymphoid tissue.

Types contra-indicating radiotherapy, best treated by operation:

1. Friable tonsils with pus and buried abscesses.
2. Repeated attacks of tonsillitis and peritonsillar abscesses.
3. Small, hard, sclerosed tonsils.
4. Fibrous tonsils with enormous hypertrophy obstructing breathing and swallowing.
5. Rapidly increasing deafness or other ear disease clearly due to pathologic tonsils.

Indications for radiotherapy as a matter of choice:

1. Hemophiliacs.
2. All malignancies of the tonsil.
3. Cardiac cases, with or without renal involvement.
4. The majority of cases of tuberculosis of the lungs or the throat.
5. Pancreatic disease and severe acidosis.
6. Severe anemias and cachectic states.
7. Diphtheria carriers.
8. Chorea.
9. Advanced age.
10. Cases refusing operations, as singers.

TECHNIC

The writer's choice, as well as that of many other workers, is radium rather than the Roentgen ray alone. The results with radium are quicker and better. Patients with cervical adenitis or with large amounts of lymphoid tissue in connection with their tonsil hypertrophy should have X-ray radiation combined with the radium therapy.

The following described technic is not suitable for the treatment of malignancies of the tonsil. In such cases at least four portals of radium implantation are needed and deep therapy to all the glands of the neck. Much larger dosage than is used in treating benign lesions of the tonsil is necessary in neoplasms. Malignant disease of the tonsil should be treated individually as no standard dosage is applicable to all cases.

Method for Applying X-Ray Therapy.—Various methods of technic are used; among the more recent is that of di Donato. The technic of Witherbee, described in the *Journal of Radiology,* 1922, is useful and with slight modifications has been used by most radiologists treating the tonsils. Judgment must be used and each case treated more or less individually.

The patient lies on the table on the abdomen with the head elevated and turned to the side, with the chin raised. The skin of the neck and face is protected with a large sheet of lead rubber or lead foil. A hole somewhat rectangular in shape, about 3 by 1½ inches, cut to correspond to the tonsil area just below the angle of the jaw, is made in the lead protector.

The dose of X-rays to produce an atrophy of the tonsil needs to be about 50 per cent of an erythema skin dose. The following description gives a suitable range for tonsil radiation: spark gap 7 to 8 inches; 5 milliamperes; aluminum filter 3 to 4 millimeters; skin distance 8 to 10 inches; exposure 3 to 10 minutes, according to the size of the tonsil and the age of the patient. This dose is repeated at two-week intervals for three or four doses. Use a cone 2½ inches square, or a circular 2-inch cone and direct the rays through the tonsil area to the lower molar tooth of the opposite side.

Atrophy will continue for some time after treatment ceases. It may be necessary to repeat the first series of treatments in about two months' time. It is better to begin with a small dose and increase gradually. Children require somewhat less than adults. Diphtheria carriers become negative usually within four to ten days with a single dose. Over 80 per cent of carriers are permanently cured by the Roentgen ray. In cervical adenitis X-ray can be given the same day the radium is used in the tonsil.

Technic of Radium Applications.—The surface of the tonsil may be painted with a 2 per cent butyn or cocain solution if the patient is very sensitive or inclined to gag. This is frequently not necessary as the application is practically painless. Five methods of applying radium have been

used successfully, the last one described (5 b), however, is the least troublesome, quickest, and the most satisfactory.

1. Radium needles of 5 to 12½ milligrams strength are placed in a special applicator (modified Corwin tonsil hemostat). Usually a total of 50 milligrams is used in such an applicator. This applicator may be screened with gold, brass or aluminum. It is covered with 1 millimeter of rubber and held against the surface of the tonsil from ten minutes to one hour according to the screening and the amount of radium used. The application is repeated in two or three weeks. Several such sittings may be necessary.

2. The application of a varnish applicator plaque of 10 or more milligrams attached to a long handle and covered with 1 millimeter of rubber and aluminum screen is held against the surface of the tonsil from ten minutes to one hour according to the strength of the plaque used.

3. The application of a radium pack externally over the tonsil may be used. Fifty milligrams or more of radium, either in tubes or needles, screened with 0.5 millimeters of silver, gold or brass and 1 millimeter of rubber are equally spaced on a 1 centimeter pithwood block and fastened to the same by adhesive. This pack is then applied over the tonsil area of the neck. It is left in position from five to eight hours according to the amount of radium used. The surrounding skin is protected with a window opening lead-rubber screen.

4. Implantation of radium needles into the tonsil tissue has been done many times. Platinum needles of 5 to 15 milligrams are sterilized and threaded with linen thread. The needle, grasped in a special holding forceps, is introduced into the tonsil tissue and the linen thread brought to the outside of the cheek and fastened with adhesive. If a 10 to 15 milligram needle is employed it should be imbedded into the center of the tonsil. The thread is fastened to the side of the cheek. The needle is left in position from three to four hours according to the amount of radium used. If needles of 5 milligrams are used, at least three or four can be placed in the tonsil tissue at equal distances. A total dosage of 50 to 75 milligram hours are used at a sitting. It is well to bury the entire needle within the tonsil tissue. The removal is extremely simple, only slight traction being made on the thread. This treatment is as a rule repeated in four to six weeks.

5. (a) A tiny bare glass tube containing 0.2 to 0.4 millicuries of radon (emanation) may be placed in the center of the tonsil with a special introducing needle. It remains as a foreign body. At times slight reaction is experienced but it is never as severe as an attack of tonsillitis and lasts as a rule only about twenty-four to thirty-six hours. Seal recommends three or four spicules of 0.28 millicuries introduced at equal distances. No unpleasant results have been reported from leaving the glass tubes in the tonsils.

(*b*) A platinum or gold radon seed containing 2.5 millicuries is threaded with a linen thread and introduced with a Muir applicator into the center of each tonsil. The thread is cut 1 centimeter from the surface of the tonsil and left protruding from the point of entry. The thread hanging down on the tonsil does not cause any interference. The seed is left in place four days and removed with grasping forceps. One dose is all that is needed. This is by far the most satisfactory method of using radium in the tonsil.

AFTER TREATMENT

Seldom is it necessary to use any local treatment to the surface of the tonsil regardless of which method is chosen. Caustic applications and metallic substances should be avoided. A mouth wash of normal salt or diluted Liquor Sodii Boratis Compositus can be used. Sometimes in poorly nourished individuals, especially in tuberculous disease where the tonsil is of Type II, the use of the ultraviolet ray directly to the tonsil with a special applicator as well as a general ultraviolet radiation will be found helpful combined with the radiotherapy of the tonsils.

The reason for failure to get relief from symptoms after tonsillectomy is due to faulty intestinal elimination, disturbed metabolism and constitutional disease. Every patient selected for radiotherapy should have a careful physical examination, including a Wassermann test, a urinalysis and, if necessary, a basal metabolism. The teeth should be put in condition. Attention should be paid to personal hygiene, plenty of fresh air and outdoor exercise. If antisyphilitic treatment is necessary, at least four months should elapse before the use of radium or X-ray therapy. Do not use radiotherapy when using mercurials, iodin, iron, bismuth, silver or other metallic medication. Most undesirable reactions may follow, especially when radium is used.

Occasionally a radiated tonsil patient does not show as much improvement as one would like; particularly is this true with the X-ray therapy, although the throat appears entirely negative. It is well to pay attention to the diet. This should contain plenty of fruit, especially the citrus fruits, green vegetables, carrots, milk, cream, eggs, liver and a small amount of other meat. A diet fairly low in carbohydrates is preferable. It is well to give a potent brand of cod-liver oil during radiotherapy treatment and even afterward. Patients subject to sore throats and frequent colds are generally low in vitamins A and D. Small doses of thyroid may be needed to keep the basal rate normal. An alkaline base diet is usually indicated with such patients.

SOME OF THE ADVANTAGES OF RADIOTHERAPY

Some of the advantages of radiotherapy over surgery, especially in patients suffering with cardiac, nephritic, diabetic or tuberculous disease

are: (1) No anesthetic is required; (2) a bloodless, painless, procedure is used with slight or no systemic reaction or loss of weight. The dose can be accurately measured and graduated to fit the needs of each individual patient; (3) no hospitalization is necessary; there is only a few hours' loss of time from work which is a very important factor with many patients; (4) singers often refuse operation and radium therapy possesses the advantage that no nasality or vocal disturbance follows its use; (5) the use of radiotherapy in chorea appears to offer many advantages over surgery and the results from radium therapy in pathologic tonsils of patients suffering with chorea have been most gratifying; (6) perhaps one of the greatest advantages of this form of treatment is freedom from lung abscesses which have of late years become somewhat more frequent with the large number of tonsillectomies performed.

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CHAPTER XXVI

THE TREATMENT OF DISEASE CARRIERS

J. E. Gordon

GENERAL CONSIDERATIONS

The patient with an acute communicable disease is largely responsible for maintaining that disease in epidemic or endemic proportions. This is true for two reasons. The infected person may transmit the disease-producing parasites to susceptible individuals, with resultant secondary cases. More commonly, the infective agent is passed to immune persons. The usual result is rapid elimination of the invader. Not infrequently, the microörganisms are maintained temporarily, at times permanently. Because of their immunity such persons fail to show the usual evidences of infection, yet are capable of transmitting the disease to others. They are human communicable-disease carriers.

Recognition of the principle that persons rather than things are chiefly instrumental in maintaining infection resulted in measurable progress in the control of communicable diseases. For many years almost complete emphasis was placed on the patient alone. So completely did this conception dominate public health practice that authorities were led to the dictum that, if at a given time all infectious material could be limited to patients then infected, communicable disease would be effectually effaced.

With many infectious diseases there is clear-cut epidemiologic evidence that duration of clinical symptoms does not parallel extent of infectivity. Bacteriological methods have confirmed these observations, and for certain diseases have made possible exact determination of the relationship for each individual patient. Similar methods applied to persons in contact with communicable disease served to demonstrate that an infectious agent within the apparently healthy human body was a phenomenon not limited to persons previously known to have had the disease. There can be no doubt that the continued existence of many communicable diseases depends to a considerable extent on the spread of the inciting agent from apparently healthy and usually immune individuals to susceptibles.

The principle of preventive medicine in relation to infectious disease originally appeared simple enough. Pathogenic microörganisms were frequently demonstrable in the discharges of the sick individual. They con-

taminated his environment. Those readily identified bacteriologically could be traced to common commodities, such as water supply, foods, and particularly milk. Limitation of infection was to be accomplished by interrupting this indirect passage of the infectious agent from the sick to the well. Thus the doctrine of disinfection dominated preventive medicine for many years. Modern sanitary practice was based on that premise. Contamination of the patient's immediate environment was corrected by terminal disinfection.

The lack of result in a final grand clean-up soon became evident. If the sick person was the originating and chief source of danger, absolute confinement to the patient of infectious secretions and discharges was more logical and offered greater protection. Medical asepsis replaced disinfection, with concurrent rather than terminal attention to infectious material. However, the person clinically ill and under proper control is not the danger often supposed. Duration of infectivity is relatively brief. The symptoms of the disease in a manner label the patient as dangerous. His activities are limited, by reason of his disability and of isolation measures.

The incomplete effectiveness of directing attention to the patient served materially to accentuate the importance of the carrier concept. Since Koch's original observation, in 1892, of a carrier state in cholera, similar conditions have been demonstrated with many other diseases, notably diphtheria and typhoid fever. Epidemiologic mysteries and failures were thereby explained. Just as appreciable progress marked the change of emphasis from disinfection to the realization of the patient as the prime source of infection, so intimate study of the carrier problem served to further facilitate control of communicable disease.

Epidemiologic Importance of Carriers.—By contrast, the carrier constitutes a more or less permanent reservoir of pathogenic microörganisms, the patient a brief one. The patient is recognized as dangerous; the carrier is apparently and practically healthy. During the World War the carrier problem first attained its important place in the general scheme of control. Some have felt that too great emphasis has been accorded it. Doubtless with certain diseases this is true; with others its importance is established. Practical methods cannot reach full development until the bacterial cause of certain important diseases has been discovered.

With cholera, the dysenteries, typhoid fever, diphtheria and meningococcus meningitis, carrier control is a recognized part of the epidemiologic method. Measles and smallpox among other diseases appear to present neither convalescent nor contact carriers, this assumption depending upon epidemiologic observations, since the causative factor remains unknown. For other diseases of an infectious nature, the problem has a probable importance, although again lack of knowledge limits definiteness. Typical of this group are poliomyelitis and scarlet fever.

Origin of the Carrier State.—Infectious diseases were considered in the earlier days of our knowledge as straight contests between host and infectious agent. Gradually it was demonstrated that in many infections there was established a kind of equilibrium in which the microörganisms remained in the host ready to multiply again when the host was off guard. Theobald Smith considers focal infections as only types of the carrier state for they represent local foci of disease toward which the host is partly immunized. In other diseases localizations occur in which the specific bacteria multiply and survive for a time in the face of complete general immunity. In such instances the individuals harboring the germs are termed carriers.

The concept of carriers is in itself complex, involving as many possibilities as there are microörganisms capable of surviving in the tissues. Certain hardy species remain within the system, others only on or in the folds and glandular structures of mucous membranes. In many instances the term "healthy carrier" is a misnomer. It is conceivable that there are temporary carriers in whom no lesion is either demonstrable or presumable. Cultures taken of attendants in the wards of contagious disease hospitals may give positive results, with negative findings later in the same day or subsequent days. Bloomfield, in his serial culture studies of normal throats, has demonstrated a more or less permanent flora, with adventitious transitory invaders from time to time.

The chronic contact carrier would seem to represent a real infection. Without multiplication, microörganisms can but temporarily maintain themselves. Food supply is essential to multiplication and it is scarcely conceivable that this is available without some actual penetration and localization within tissue. This may represent primary invasion in the naturally immune host. At times it would seem to depend upon reinfection. A boy, seven years of age, had had scarlet fever three years previously. It is possible that he may have remained a convalescent carrier. It is probable that he did not. No cases were traced to him. He acquired a sore throat without other pertinent symptoms. Within the next eight days, two sisters of preschool age developed scarlet fever. The boy was shown to have a tonsillitis due to specific scarlet fever streptococci. His carrier condition persisted six weeks and was terminated by tonsillectomy.

Definite anatomic changes can most frequently be observed in the chronic convalescent carrier. In fact, diligent search will usually demonstrate them. Recovery from the disease can be assumed to have been accomplished by a general immunity, which, in the process of overcoming the widespread bacterial invasion, has accomplished a localization or walling off of some particularly resistent focus. While this is rendered innocuous by the assumption of balance between infection and resistance, it persists for long periods of time. The healing process in tuberculosis and syphilis is illustrative. For carriers of upper respiratory diseases or those gaining

entrance to the body by that tract, the usual lesion is of the faucial tonsil, although other structures of that region may be affected. The gall-bladder occupies a similar position with respect to organisms discharged from the alimentary tract.

Classification of Carriers.—For practical purposes, human disease carriers may be considered of two types. The convalescent carrier is the more important, because of the commonly protracted course. The second group includes those persons never having had the disease, at least in recognizable form, in whom the carrier state arises through contact with a patient or another carrier. These are often termed healthy carriers, but the limitations and frequent incorrectness of this term have been emphasized. To these may be added a third, the so-called incubationary carrier of Nicholls, but whether this group should be considered true carriers or actual patients whose symptoms are unrecognizable by present methods is disputable. Epidemiologic practice further differentiates temporary and chronic carriers in the two major groups; in addition to these, there are presumably relapsing carriers. Whether the relapse is actual or in degree and dependent upon faults in bacteriologic technic cannot be proven. Finally, with carriers as with patients, there are mistaken diagnoses, so-called "laboratory carriers" or pseudo-carriers, arising from confusion of bacterial species.

Virulence of Parasite in the Carrier State.—The actual clinical importance of any given carrier must in the final analysis rest upon the virulence or disease-producing power of the particular parasite carried. Certain strains of specific microörganisms lack virulence. Studies on bacterial dissociation seem to emphasize that probably no pathogenic bacterium is without its variants. Subjection of more or less strictly parasitic species to conditions of artificial culture may serve to gradually effect changes into almost non-pathogenic types. Similar changes among pathogenic organisms are probably induced in the human and animal body. Since the organism must meet in the tissues a variety of obstacles, particularly in the generally immune host, the parasite must adapt itself or else cease multiplying.

Thus it is logical to assume that in many instances a gradual attenuation of the carrier strain is going on which is proportional to the period since convalescence, and that the most virulent types are the ones transmitted during or immediately at the end of the acute disease process. Diphtheria bacilli from throats of carriers have been found atoxic at variable periods after symptoms have subsided.

The practical application of probable variation in virulence to management of carriers is handicapped in several ways. For many bacteria there is no laboratory method of determining virulence. At best virulence is measured in an alien species, which is naturally insusceptible. Furthermore, there is no way of determining the behavior of a microörganism

judged non-virulent under environment in an immune host, if it be trans-
ferred to a susceptible one.

Diagnosis of Carriers.—The actual diagnosis of a carrier depends
upon laboratory methods. Vaughan has well stated that one of the greatest
contributions of bacteriology to epidemiology is the teaching about carriers.

Determination is in general more difficult than with cases. Admixture
with other organisms and relative infrequency in numbers complicates
bacteriologic diagnosis, although cultures from chronic carriers may have
surprisingly pure growths. The actual number of persons to be examined
increases the technical difficulties but an immense amount of unnecessary
work and great saving in time when it may mean much can be contributed
by proper interpretation of epidemiological considerations, combined with
careful clinical examination of suspected persons. A person with hyper-
trophied tonsils suggests a diphtheria carrier; clinical cholecystitis would
direct suspicion in the search for a typhoid carrier. Clinical methods are
of greatest value after bacteriologic diagnosis has been made. Localiza-
tion of the infected focus is essential to successful treatment.

Management of Carriers.—The management of a demonstrated carrier
requires that primary consideration be given to the prevention of further
cases. Seemingly a most practical procedure in a given epidemic consists
in directing attention to those carriers who are found directly associated
with clinical cases and largely disregarding others, who may be found
in any general population and often indeed are pseudo-carriers or individ-
uals infected with non-virulent parasites. Actual medical management
is often discouraging and protracted. The principle that terminal or hold-
over stages of infectious processes are the most difficult to deal with
therapeutically applies no more tritely than in the management of car-
riers, particularly the convalescent carrier, who represents the ultimate
in terminal stage. The patient is essentially in good health, and requires
treatment not so much from his own standpoint as that of others. Altruism
is a characteristic all too infrequent without direct application to friends
or family or self. The carrier resents restriction of his movements and
economic loss from unemployment.

CARRIER GROUPS

In conformity with the practical division of diseases as they affect
important anatomic systems, carriers may be classed as respiratory, ali-
mentary, circulatory or sexual. Such classification, as with disease proc-
esses, is arbitrary but indicates generally those carriers in whom the
infectious agent has gained entrance and is eliminated by one of the
major systems of the body.

Understanding of carrier conditions is perhaps most completely devel-
oped in the alimentary group. The existence of the carrier state was first

determined by Koch in cholera. Typhoid bacillus carriers have been extensively investigated and may serve as the type within this group.

Typhoid Bacillus Carriers.—If many cases of typhoid fever develop in a community within a relatively brief time, attention is directed toward a contaminated milk or water supply. On the contrary, if the disease is characterized by localized outbreaks with sporadic cases and difficulty in tracing their origin, the likelihood of carrier transmission is apparent. Present-day hygienic protection of common water and food supplies has tended to increase the relative importance of carriers in a fast dwindling disease.

Guided by his work with cholera, Koch, in 1902, advanced a similar hypothesis to explain certain obscure cases of typhoid fever. He felt that typhoid bacilli might persist in the gall-bladder of convalescents for years after an attack of the disease and be eliminated in the feces.[1]

With typhoid fever, bacteriologic recovery fails to correspond with clinical recovery. In the fourth week of typhoid fever somewhat more than 10 per cent of patients have positive cultures. According to Lentz about 4 per cent of all typhoid convalescents become permanent carriers. The frequency is far greater for women than men, in the ratio of about four to one.

The condition is not confined to convalescents from the disease. Among 1700 apparently normal persons who had been in contact with cases, Klinger found twenty-three to be carriers. Eleven had never had typhoid; twelve gave a history of likely antecedent attacks. Of the twenty-three, twelve were permanent carriers. It has been estimated that 0.3 per cent to 0.4 per cent of the population of large cities are typhoid carriers. Simon feels that perhaps 40 per cent of all present-day cases can be attributed to contact with carriers.

The habitat of the typhoid bacillus in the carrier is fundamental to diagnosis and to management. The organisms are eliminated by bowel, less frequently in the urine, at times by both. They have been demonstrated at autopsy throughout the intestinal tract, but are always found in the bile, usually in pure culture and in large numbers. The continued carrier state depends upon the development during the acute stage of the disease of cholecystitis, which subsequently is oftentimes complicated by cholelithiasis. From this source, bacilli are discharged into the intestinal tract, and probably cannot there be maintained in the absence of continued reënforcement from the gall-bladder. Urinary carriers are scarcely one-tenth as frequent as intestinal. Lesions of the kidney pelvis, more commonly a cystitis, have been demonstrated as the focus.

Search for carriers may include the wholesale examination of a suspected group, if it be not too large. More commonly it is essential to

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[1] Welch and Blackstein had demonstrated in 1891 that in rabbits inoculated with typhoid bacilli the organisms survived in the bile for long periods.—Editor.

limit efforts to immediate contacts, and certain individuals who excite direct suspicion. These include persons with a history of previous typhoid fever, particularly women; individuals with a demonstrated Widal reaction; and all who complain or have complained of symptoms however slight in connection with the gall-bladder. Food handlers with these symptoms definitely come under suspicion. The Widal test is a more simple laboratory procedure than bacteriologic examination of feces and urine, and may serve to eliminate many suspects. Those with positive Widal tests require examination of excreta for typhoid bacilli. If there is good evidence connecting a suspect carrier with a case, repeated examination of the stools is necessary whatever the result of the Widal or initial cultures. Bile flow may be increased by cholagogues, followed by mild laxatives. Most satisfactory results are obtained by examination of material removed directly from the duodenum.

Control of the carrier problem in typhoid fever is dependent upon release of active cases only by culture. If a convalescent patient is discharged as a carrier, public health authorities should be so notified, that his subsequent activities may be properly checked. Members of the family must be immunized with typhoid vaccine. If the condition is of some duration they probably are already immunized, through natural process or attack of the disease. No preparation of food by these carriers for public consumption can be permitted. Violation of this requirement constitutes a real danger. Instruction of the affected carrier in his personal habits, the nature of the carrier state and his potential danger to others is essential. Proper care of fecal discharges by addition of lysol, and satisfactory disinfection of the hands are the important factors in personal hygiene.

From the standpoint of responsibility, the care of demonstrated chronic carriers is a state problem and cannot logically be considered a responsibility of the local community nor of the individual himself. The protracted course prevents hospitalization. They cannot be committed to homes for the poor or destitute. In several states such persons are subsidized, located in more or less isolated communities and furnished opportunity to contribute to their own support. Every effort should be made to deprecate publicity about carriers, first because it renders control of the patient more difficult and secondly because it engenders troublesome hysteria in the community.

Every effort should be directed toward medical management of the carrier. Certain cases prove absolutely refractory, but results are by no means as hopeless as sometimes supposed. Certain disappointments may be prevented if measures proved inadequate are eliminated from consideration. Intestinal antiseptics are valueless as would be expected, since the gall-bladder is chiefly affected. Any effect on bacilli temporarily present in the intestine can lead to no permanent benefit. Cholagogues have

no effect on the actual lesion in the gall-bladder. Administration of vaccines with the purpose of increasing general resistance is illogical because the carrier already has a high-grade general immunity. Typhoid antibacterial sera have been ineffectual. Chemicals with supposed antiseptic effect on kidney secretion, as urotropin and hexylresorcinal, have irregularly been conceded therapeutic effect but average opinion discounts their effectiveness.

Remedial measures must be directed toward the source of the bacilli, which is the pathological gall-bladder. Surgery is the one measure which offers any regular promise. Dehler, in 1907, reported two cases upon whom he performed cholecystotomy with temporary but not permanent results. Actual extirpation of the diseased organ has, however, been generally successful. This would at first hand appear drastic therapy for such an innocuous condition. Aside from public health considerations, such procedure can be recommended to the carrier, in view of his probable prolonged quarantine with attendant social and economic sacrifices. Cholecystectomy usually corrects the condition. It may fail because of multiple foci of infection and the fact that in a minority of carriers the focus is not in the gall-bladder itself but in the biliary tract. An appreciable portion of convalescent chronic carriers recover spontaneously within six months following the actual attack. The procedure should not be advocated within that interval. Nicholls reports chronic urinary carriers relieved by nephrectomy.

Dysentery Bacillus Carriers.—The distinguishing feature of these carriers is localization of infection in chronic ulcers of the bowel. Carriers are not only less frequent than in typhoid fever or cholera, but the course is less chronic. Diagnosis is more difficult because organisms are discharged in smaller numbers and not as regularly. Convalescent cases still discharging mucus even in the absence of bacterial findings may well be considered potential carriers.

Cholera Spirillum Carriers.—The infectious agent of this disease is maintained in convalescents for a shorter time than in convalescents from typhoid fever. Only exceptionally are spirilla demonstrable in feces beyond the second week. Contact carriers are somewhat more frequent, but they likewise tend to be temporary. Probably 3 per cent of all cases terminate in the chronic carrier condition. Chronic cholecystitis determines the existence of the carrier state and is the source from which organisms are discharged into the bowel. Urinary carriers have been observed but less commonly than with typhoid.

Cholera carriers more commonly clear spontaneously than do typhoid carriers. Surgical methods may well be considered if the condition persists.

Diphtheria Bacillus Carriers.—As early as 1890 Escherich found diphtheria bacilli in the throat after the symptoms of diphtheria had subsided and the membrane disappeared. They may remain for days, months

or even years, but the convalescent carrier condition as a rule is relatively brief. In Detroit, an average of three thousand diphtheria patients had their first of two successive negative cultures on the seventeenth day. About two-thirds became bacillus free within two weeks. By the end of a month 85 per cent of cultures were negative. Less than 2 per cent persisted after two months.

Park has estimated that about 1 per cent of the total population are carriers of virulent Klebs-Loeffler bacilli. For children the frequency would probably be twice as great. Among direct contacts with diphtheria the incidence is greater, varying from 10 per cent to 20 per cent. An essential difference distinguishes contact and convalescent carriers. With contact carriers the condition is usually temporary, while convalescent carriers tend to a longer course and include most chronic carriers.

While other lymphoid structures and mucous membranes of the nose and throat may be involved, the localized infection responsible for the chronic carrier state in diphtheria is almost exclusively limited to the faucial tonsil. Histologic examination of tonsils from diphtheria bacillus carriers demonstrates that the infectious agent may be limited to the surface epithelium, but more commonly penetrates deep within the crypts leading to well-marked inflammation and formation of a fibrinous exudate, which is extruded heavily infected with bacilli. Some carriers discharge the organisms from the nose alone. A chronic inflammatory or atrophic process of the nasal mucosa is usually present; occasionaly there is extension to the accessory sinuses. Foreign bodies in the nasal passages give rise to local irritation and prolong the carrier state. A child four years old had been a nasal carrier for nearly a year. Removal of a shoe button led to recovery within ten days. The middle ear is a less common focus. Discharging ears of whatever etiology often become secondarily infected with diphtheroids, as the condition becomes chronic. The organisms are not true diphtheria bacilli but lead to no little confusion. By careful physical examination of the nose and throat, locally infected areas or structural anomalies can regularly be demonstrated as the underlying cause of the chronic carrier state.

Diagnosis of diphtheria bacillus carriers depends purely upon bacteriologic evidence. Certain essentials in obtaining material are well emphasized. Small swabs are better than larger ones and are to be stroked over the tonsil and pressed into the opening of crypts. Nasal swabs must be introduced well into the posterior nares. If that is impossible because of obstruction of the passage, bent wire swabs of the Mathers type should be introduced into the nasopharynx.

Requirement of release of patients from isolation by cultures from the nose and throat is essential to control of the carrier situation. Two successive negatives twenty-four hours apart are practically sufficient to prevent disease spreading. It would seem advisable to maintain strict

isolation of early convalescent carriers and of all contact carriers. The condition will likely clear within a reasonable time. When it becomes apparent that the carrier has developed the chronic state and is not responding to treatment, it is advisable to modify accepted regulations. With proper coöperation on the part of the patient and a well-grounded sense of responsibility this can be accomplished without hazard. In Detroit, chronic carriers are released from quarantine under treatment and permitted to take up outdoor work in which they do not come into contact with other workmen. Some carriers have special jobs in factories, not bringing them into contact with large groups. They are not allowed to use public conveyances and hours of work are such as not to coincide with the coming and going of other employees. Duties concerned with food handling are not permitted. Children must be kept out of school.

Carriers should be considered as harboring virulent organisms until disproved. About 90 per cent of convalescent carriers are virulent up to three months after the acute infection. Early contact carriers are usually so. If the carrier be neither convalescent from the disease nor in recent contact with a patient, the chances are the organism is avirulent. Survey of such a group showed scarcely more than 10 per cent to be carriers of true virulent bacilli. For the latter group, a determination of virulence should be made immediately. In general, if the carrier state continues longer than three weeks for contact carriers, or a like period after clinical recovery for the convalescent type, similar virulence tests are indicated. Most of the first group, a measureable proportion of the other two, may be released with practical safety. An organism may undergo progressive decrease in virulence under the unfavorable environment of the immune host. Consequently successive virulence determinations should be made at intervals of a month. An appreciable number will ultimately become negative.

Local treatment of the infected focus is to be instituted as soon as the condition is diagnosed. This is often unsatisfactory. Some discredit such measures entirely and consider cases terminating favorably to have undergone spontaneous recovery. However, a group of early carriers receiving no treatment was compared with a similar group under local treatment. The latter cleared up more promptly. Such treatment also tends to keep the patient satisfied until such time as more radical measures are possible or indicated. To one who has much to do with the treatment of carriers, that is no unimportant consideration. The carrier is not ill, often does not appreciate the seriousness of his condition from the standpoint of the public health, is undergoing real economic sacrifices because of his isolation, and in general is an uncoöperative and disgruntled patient.

As far as local applications are concerned any result to be expected from a particular drug will probably be evidenced within a week of inten-

sive use. Ordinarily argyrol in 20 per cent solution is first used, the tonsillar area being thoroughly swabbed every four hours. If results are not obtained within a week, 2 per cent iodin in glycerin is substituted. Silver nitrate in 10 per cent aqueous solution is the most efficient of topical applications, but is advocated only after other measures have failed. Because of its corrosive action, it can be applied only to limited areas and for brief periods. Applications twice daily for five days, with interruption of the treatment for a similar time, is suggested. Nasal carriers sometimes are relieved by application of 5 per cent phenol in glycerin to the nasopharynx by means of the curved wire swab. Nasal drops well instilled, of the formula mercurochrome 0.3, alcohol 4.0, glycerin 4.0 in water to make 30 c.c., have seemed to yield results. This also is mildly irritating and not to be used too long. Cultures are to be continued during the course of treatment. Release may be recommended with two negative cultures after treatment has ceased.

Many other measures have been extensively investigated with absence of results. Antitoxin has no effect on the carrier state. Diphtheria bacillus vaccines and antibacterial diphtheria serum are without value. Kaolin insufflation has been discarded. Attempts to implant lactic acid bacilli, *Bacillus pyocyanus* and staphylococci in the affected throat with the purpose of overgrowing the more delicate pathogen are without permanent result. Repeated treatments with Roentgen rays sometimes give results, through shrinking lymphatic tissue rather than any antiseptic action. Ultraviolet light treatments offer more promise but chronic carriers are notably resistant. The treatment is more likely to be successful when the organisms are present in the throat than when in the ear or nose.

The one measure that offers relatively certain relief is tonsillectomy. A previously performed tonsillectomy should not detract from careful examination of the fossæ for stumps or tags of lymphoid tissue. Too frequently tonsillectomy is incomplete. The operation is not to be advised until at least six weeks have elapsed since the attack of diphtheria, on account of the well-known effect of diphtheria toxin on the heart muscle; then only if there have been no clinical signs of myocarditis. Three to six months is a safer limit. Results are most satisfactory. As a rule bacteriologic examination of the nose and throat will show freedom from bacilli within ten days. Relatively few cases extend beyond that time, and in a rather large experience no failures have been noted. One patient continued positive findings for twenty-four days after tonsillectomy, following which he had three negative cultures. Such failures as occur are due to multiple foci, a primary focus other than the tonsil, or incomplete removal of tonsillar tissue. Simple mastoidectomy may be required for chronic ear carriers.

Scarlet Fever Streptococcus Carriers.—An outstanding characteristic of scarlet fever is the extreme duration of infectivity during convalescence.

Complications are frequently responsible for this, the most significant being rhinitis and sinusitis, and discharges from the middle ear. All suppurative discharges are potentially infective and require an extended quarantine. Less definite information is available concerning the uncomplicated case. That infectivity is long continued is apparent from accepted quarantine regulations, which vary from four to six weeks after onset.

The discovery of a specific streptococcus as the cause of the disease makes possible more accurate knowledge of scarlet fever carriers. Ker's prophecy of years ago that great advances in control of scarlet fever would be possible when quarantine could be determined by bacteriologic methods is likely to be justified.

Quarantine based on an arbitrary elapsed time requires too long restriction of certain patients and for others the legal limit is insufficient. Undeveloped bacteriologic methods prevent application of known facts. Other hemolytic streptococci distinct from the specific type of scarlet fever are found in the normal throat and in non-specific diseases of the upper respiratory tract. Their differentiation can be accomplished, but the process is too technical for practical application. Absence of all hemolytic streptococci from the nose and throat of convalescents is, on the basis of Dick's work, evidence of termination of the carrier state. Such patients have been safely released. Continuation of quarantine because of persistent purulent discharges would appear unnecessary in the absence of the specific streptococcus. All convalescents from scarlet fever, who harbor hemolytic streptococci, are not necessarily scarlet fever carriers. In the face of a long continued apparent carrier state, type specificity can be determined, a procedure quite comparable to virulence determination in diphtheria control work.

The actual determination of true contact carriers has not been reported, but it is well known that in scarlet fever epidemics there is an increase in the hemolytic streptococcus index among the general population. More detailed studies with recently developed bacteriologic methods offer interesting possibilities.

Management of the scarlet fever carrier is to our knowledge directly comparable with that of the diphtheria carrier.

Meningococcus Carriers.—During the last extensive outbreak of epidemic meningitis in 1918, a great deal of emphasis was for the first time placed on carriers of the meningococcus. Adequate methods and sufficient trained personnel were available to study a feature of such epidemics hitherto largely unexplored. The general carrier rate among exposed populations reached unbelievable limits, in some instances as great as 50 or 60 per cent. In some military units, scarcely enough unaffected individuals remained to guard the carriers. Segregation of all carriers, even their identification, soon became manifestly impossible. Probably the resulting conclusion from an immense amount of work was that one

need not be too greatly alarmed about carriers in this disease. The condition is usually temporary. If persons in contact with the disease are properly spaced out, so that crowding is eliminated, the carrier rate drops appreciably. Contact carriers clear up rapidly under good hygienic living conditions.

Local treatment of persistent meningococcus carriers is relatively ineffectual. The locus of infection is the nasopharynx, rather than the tonsil, and this region is rather inaccessible. The chronic condition is many times associated with involvement of the nasal sinuses. Surgical drainage has corrected some of the most obstinate cases.

Other Respiratory Carriers.—Pneumococcus carriers have been demonstrated but their practical relation to the spread of the disease is not well understood. Carriers of streptococci have been implicated in extensive epidemics of respiratory diseases. Whooping-cough is an unexplored field. Epidemiologic evidence implicates carriers prominently in a number of the more common communicable diseases, mumps, poliomyelitis, encephalitis, influenza, and the common cold, but identification and control must await discovery of the infectious agent.

CHAPTER XXVII

POISONING FROM ANILIN, NICOTIN AND COSMETICS

Joseph C. Doane

ANILIN POISONING (ANILISM)

Introduction.—Anilin poisoning represents a comparatively recent industrial hazard in the United States.

The English word "anilin" is derived from the Arabic "an-nil," meaning indigo. Although anilism has greatly increased in incidence in the past decade, due to the interruption in the importation of dyes, occasioned by the World War, yet, as early as 1873, Carrol reported a case of local poisoning from the wrist-band of a glove, colored with anilin dye; and Murray, in 1877, described a similar poisoning in a child of three and one-half years, who wore for but one day a pair of scarlet-colored hose.

The tragic death of Professor Wirtz, of Paris, who, while demonstrating the properties of anilin as a coloring matter, inhaled its fumes in such concentration that he almost immediately succumbed, demonstrates both the possibility and the gravity of this method of poisoning. A similar but less serious toxicosis, as a result of the inhalation of the fumes of anilin, was reported by Baily, in 1872.

Anilin is manufactured by bringing hydrochloric acid and iron filings in contact with pure nitrobenzol. It is a colorless, oily, inflammable liquid, of a peculiar odor and a burning, aromatic taste. It may become brown on standing. It boils at 184° C., and is freely soluble in alcohol, chloroform and ether, but sparingly so in water.

While anilin and its sulphates have been used by the physician in the treatment of certain diseases, notably epilepsy and chorea, it finds its greatest usefulness when combined with such substances as chlorin and the chlorates, to form the anilin dyes so essential to the textile industry.

Anilin and nitrobenzene are used in the manufacture of rubber, and of certain washes for printing-press rollers. It is a basic component of dyes and coloring compounds, such as shoe polish. Indeed, early cases of poisoning were in persons who, no doubt, were hypersusceptible to the drug and who manifested serious symptoms after having their shoes shined with an anilin-containing preparation. It is used as a coloring substance in the manufacture of certain kinds of lead pencils, and also in indelible inks.

Anilin colors are used for the dyeing of leather, water-soluble preparations being most commonly employed. To produce a black vegetable tanned leather, certain coal-tar blacks, chiefly nigrosin, are used. Anilin is now being used as a substitute for vegetable, arsenical or other mineral colors, in the dyeing of furs, feathers and artificial flowers. Wall paper is almost exclusively dyed with anilin. In the printing industry, the demand for bright colors has increased the use of anilin dyes, and has, hence, augmented poisoning with this chemical. It is not to be forgotten that chemists, physicians and laboratory technicians are often exposed to this danger during the prosecution of research work, particularly along bacteriological lines.

As has been intimated above, most of the poisonings by anilin have been observed in industry and have been caused, not by anilin alone, but by anilin oil, which contains anilin, toluidin, nitrobenzene and other benzene derivatives.

The source of such toxicoses has been largely by absorption through the skin, as a result of the contact with clothes impregnated with the drug. Inhalation is another method by which the poison reaches the blood stream.

As has been already intimated, absorption through the skin and the mucous membranes is the most common method of poisoning. These portals of entry may both serve as sources of poisoning to workers, inhalation as well as absorption through the skin taking place at the same time. High temperatures seem to favor poisoning. Poor ventilation and improper instructions to workers, as to the best methods of protecting themselves against harm, are also important factors.

As an example of the industrial incidence of this poisoning, out of 128 cases of occupational disability produced by chemicals in a German dye factory, 109 were due to anilin. Shoemakers have been poisoned from handling shoes dyed with anilin-containing preparations. Muehlberger, in 1925, reported a series of ten cases of shoe-dye poisoning, making a total of fifty-eight cases described in the medical literature to that date. Patek, in 1926, added to this number a report of three cases, who were poisoned by anilin-containing shoe polish. R. E. Cloud reported the following interesting case, representing a toxicosis as a result of poisoning from shoe dye:

Nellie M. had her shoes dyed at 5 p.m. Three hours later, blueness of the lips was noticed by her mother, and her appearance soon became alarming, her face and hands being very pale, and the lips and fingernails increasingly cyanotic. The child became very irritable and behaved as if extremely tired. The heart was regular, the pulse, 134, a systolic murmur was heard over the precordium. The physician detected the odor of freshly dyed shoes, and removed the patient to the fresh air. Convalescence was uneventful.

Infants have shown serious toxic symptoms from wearing diapers marked with anilin ink. Neuland has reported the poisoning of two in-

fants, who were observed to be cyanotic, and in whom it was suspected that a congenital heart lesion existed. The curious coincidence of two such cases, arising at the same time, aroused a suspicion that this surmise was incorrect. It was later found that anilin ink had been used to stencil laundry marks on the diapers and other clothing of these children, and that poisoning had resulted therefrom.

Anilin, in some instances, has been employed as an agent of self-destruction.

Feather dyers are subject to poisoning when anilin, or any agent of the benzene group, is found in the coloring matter used. Kilgore reports the case of a young woman, so employed, who presented a red-cell count of 12,400,000, and a man, who was likewise employed in coloring feathers, who also had a marked polycythemia. Athletes have been poisoned from their contact with anilin-containing marking ink, which was used to stencil ordinary "sweater shirts," commonly worn in training. Dame Fashion exacts tribute at times from those who would transform the appearance of the hair and mustache by the use of dyes. Cosmetics are likewise anilin-containing at times. Close-fitting, dyed hats and neck furs, and the wearing of dyed fabrics, or their use as draperies or hangings, have resulted in anilism. Eighty-six cases of fur dermatitis have been reported by Roxburgh, although no information is at hand as to how many of these cases were due to anilin. Luce and Hamilton believe that the young are more susceptible than the old, blondes more than brunettes, and alcoholics more than abstainers.

There appears to be no doubt that there is to be found an individual resistance to poisoning by anilin, since in some dye factories men employed in identical processes with comparable precautions are most unequally affected.

General and Constitutional Symptoms.—Two general types of poisoning may be described: (1) The local effect which arises from contact with articles of clothing colored with an anilin-containing substance; and (2) a general or constitutional toxicosis, which results from the inhalation of anilin fumes, or the ingestion of the drug in solutions of commercial dyes.

These symptoms may vary from a troublesome, but relatively harmless dermatitis, to a sudden prostration, with rapidly developing coma and prompt dissolution. They may be acute or chronic in type, depending upon the duration of exposure. The amount of drug which has entered the circulation, as well as the susceptibility of the individual patient, play a rôle.

Local Symptoms.—The dermatitis, which is manifested by one poisoned by anilin, is usually found at the point at which the anilin is brought in contact with the skin. The lesion consists of a vesicular or pustular dermatitis, which is characterized by intense itching, moderate swelling,

edema and gradual subsidence under treatment, or when the anilin-containing garment is withdrawn.

Thibierge and Lacassagne have reported six cases of an eczematoid eruption, due to the wearing of dyed furs. This eruption appeared sometimes in the form of mere red patches, accompanied by a slight edema of the skin. Crusts, with later desquamation, resulted, if the dyed garment was long kept in contact with the skin. These disappeared on cessation of exposure, but reappeared when the fur was again applied. It appears that the skin of habitual drunkards becomes easily inflamed when exposed to the fumes of anilin. The wrists and hands, from wearing woolen gloves; the legs and feet, from stockings; the forehead, from a colored hat-band; and the body, from dyed undergarments, have all been reported as sites of anilin dermatitis.

The local signs usually appear in from twenty-four to forty-eight hours after anilin has been brought in contact with the skin. There is sometimes observed tumefaction of adjacent glandular structures, and desquamation occurs over the affected areas, after recovery from the acute stage.

Constitutional Symptoms.—Mild constitutional symptoms, however, may be combined with the above described local signs; or, on the other hand, the latter may predominate, and the former be of importance only as a diagnostic signpost.

If poisoning takes place as a result of inhalation, symptoms develop more rapidly than when the chemical reaches the blood-stream through the gastro-intestinal tract. As will be noted, the basis for the production of many of the special symptoms from anilin poisoning lies in the interference with internal respiration. As a result of this interruption in the transportation of oxygen by the red blood-corpuscles and the formation of methemoglobin, the following train of symptoms is observed:

1. The patient has an almost corpse-like appearance, the face and body being of a leaden hue. The lips, tongue and conjunctivæ are of a grayish pallor.

2. The respirations are gasping.

3. Consciousness may be retained until just before dissolution takes place.

4. The pulse is small and irregular.

5. The patient complains of a racking headache.

6. The blood will be found thicker than normal and of a chocolate color.

In the industrial cases of acute poisoning, the symptoms may come on suddenly, or may not appear for several hours after the individual has left his work. In the rubber industry, for example, the following symptoms of chronic anilin poisoning have been described:

The face was flushed, and the patient complained of fatigability and

mental confusion. The disposition became irritable, and headache, dizziness and nausea were not infrequently the subjective symptoms present. The patient presented varying degrees of cyanosis, and complained of a constant sensation of being cold. The pulse was rapid and weak, the rate becoming depressed and the blood-pressure lowered.

These patients complained of a choking sensation in the throat, and a burning, stinging sensation of the eyelids, as well as joint and muscle pains. Painful urination, alternating constipation and diarrhea were present.

The striking feature in this group of patients was the marked pallor of the skin and the cyanosis of the lips. The characteristic odor of anilin was observed in this series of cases. In cases in which the amount of the drug absorbed has been massive, the symptoms presented have been stormy in nature, and have represented a much greater hazard to the patient. Consciousness may be early lost, and delirium and epileptiform convulsions manifested. The mucous membranes may appear almost black in color, while the respirations are slowed, and the heart's action is rapid and feeble. Nausea and vomiting may occur; the pupils are contracted or dilated, in the former instance failing to react to light. The skin is cold to the touch, and bathed in perspiration. There is ofttimes dysuria, and the urine is smoky in color, containing anilin and methemoglobin. The spectroscope reveals a characteristic band of the latter substance in the blood, and granular basophilia and stippling of the red blood-cells are observed.

When the above symptoms occur in less intense degree, the picture of chronic anilism, already described, may be presented.

Whenever a worker in industry, in which this chemical is employed, presents frontal headaches, tinnitus, anemia, vertigo, mental confusion or a delayed response to questioning, with periods of nausea, vomiting and diarrhea, the diagnosis of anilism should be suspected.

Poisonings do not occur in industry only. Thrifty housewives sometimes purchase dyes for the recoloring of personal wearing apparel, and poisoning has been known to result in this way.

The type of anilin ingested determines in a way the degree of poisoning therefrom, the free alkali being much more toxic than the salts of this chemical.

Chemical Isolation of Anilin.—*Isolation.*—The general method of distillation is used, but instead of acidifying, the material is made strongly alkaline with NaOH. The anilin easily passes over into the distillate, which is tested as follows: If the distillate is shaken out with ether, and this ether layer is then separated from the aqueous layer and allowed to evaporate, drops of colored anilin remain as the residue.

Tests.—The distillate is alkaline, has the characteristic anilin odor, and may contain oily drops.

1. On the addition of a small quantity of a solution of bichromate of potassium to a drop of concentrated sulphuric acid that contains a trace of anilin, a blue color slowly appears, which persists for many minutes and finally disappears. In the presence of more or less water, the color is either green or black, according to the concentration, but under no condition does the blue color pass rapidly through purple into red.

This reaction for anilin, which is conveniently made on a white porcelain surface, involves the same reagents as are used in the principal color reaction for strychnin, and in trials for poisoning by strychnin, the analyst is sure to be annoyed with the senseless questions concerning anilin, questions that could be asked only by a person who had never performed the reaction with both substances.

2. On the addition of a solution of calcium hypochlorate to a solution of free anilin, a violet color is produced, which, under certain conditions of concentration, passes through the shades of purple into a dirty red. With a solution of 1 : 10,000 the violet color is pale, or does not appear at all, but on the addition of a few drops of very dilute ammonium sulphid, a rose-red color is produced, even when the original solution contained only one part of anilin in 250,000 parts of water.

3. To 5 c.c. of the distillate, add two drops of chloroform and 2 c.c. of alcoholic potash solution. On warming this mixture, the disagreeable and pungent odor of phenylisocyanid appears, if anilin was originally present.

4. Anilin salts, in great dilution, yield with bromin water a flesh-colored precipitate of tribromanilin.

5. Evaporated with nitric acid, it leaves a red residue.

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CHRONIC NICOTIN POISONING

Introduction.—In an article printed in the first edition of this work, the subject of acute nicotin poisoning was discussed. It is our purpose to set forth in this chapter some facts relative to chronic intoxication by nicotin, with particular reference to the effects on the human mechanism of the tobacco consumed by the pipe, cigar and cigarette smoker.

In the former article (Vol. III, p. 671), the incidence, symptomatology and treatment of the toxic ingestion of nicotin in solution were considered. The symptoms resulting from this type of intoxication are dramatic in onset, and frequently serious in outcome. In chronic nicotin poisoning, as exemplified in the habitual smoker, the symptom picture is much less striking, and, in the light of our present knowledge, the results are much less easily prognosticated.

That smoking seems to be increasing among all strata of society appears evident. This, it has been said, is particularly true among the inhabitants of certain of the countries which were participants in the World War. Particularly in the United States has the practice of cigarette smoking extended to all grades of society and to both sexes. Perhaps too short a space of time has elapsed—during which there has appeared to be a marked increase in the consumption of cigarette tobacco—to fairly judge the effect of excessive smoking, particularly upon the youth of this nation. Nevertheless, there are some writers who contend that this habit is bound to exert a deleterious effect upon subsequent generations.

In contrast to the above statement relative to a probable increase in the use of tobacco in the United States, one views with interest a statistical study of the *per capita* consumption in Sweden during the past seven decades.

In 1856, seven-tenths of a pound of tobacco was consumed annually by each individual of the above-mentioned nation. In 1926, the *per capita* consumption was one and four-tenths of a pound, there being but little fluctuation in this rate in the past half century. It is interesting to note that in the city of Stockholm, in the past sixty years, the consumption, *per capita,* of coffee has increased 450 per cent.

It is difficult to estimate the exact rôle which gaseous impurities in tobacco smoke play in producing the symptoms commonly ascribed to nicotin poisoning. Even granting that nicotin may be the chief offending ingredient in tobacco smoke, there still remains ample proof that carbon monoxid, the aldehyds and collidin are capable of producing more or less toxic symptoms. Very much less definite statements can be made in regard to the concentration of these substances in tobacco smoke generally. Armstrong believes that cigarette smoke usually contains one per cent carbon monoxid, while a rapidly consumed Havana cigar may contain, in its smoke, at least 8 per cent of this poison. Dixon has demonstrated that the

blood of cigarette smokers may contain at times as much as 5 per cent of carbon monoxid. The smoke from pipes is said to contain the greatest percentage of nicotin, and cigars and cigarettes lesser quantities, respectively. This observer believes that the ill effects of cigarette smoking are chiefly due to carbon monoxid, while the smoking of cigars produces, in the main, symptoms, if at all, as a result of a toxic nicotinism. It has been stated that smoke from Kentucky, Virginia, Havana and Maryland tobacco contains 8, 6, 5, and 2 per cent of nicotin, respectively.

Chronic nicotin poisoning may also occur in workers in tobacco factories, who inhale the dust arising in the course of the handling of this product.

It is but a matter of historic interest to recall that J. M. Deacon has reported a variety of malingering in the French Army, which was brought about by placing cheroots in water for a number of hours, and then in each axilla at bedtime, in order to produce a disabling dermatitis, and a mild systemic poisoning. Another author describes poisoning which has resulted from soldiers placing their tobacco inside of tight helmets or caps, and thus producing toxic absorption. It appears that the inhalation of tobacco smoke increases the incidence of chronic poisoning, and there seems to be sufficient evidence at hand to substantiate this statement.

Chief Presenting and General Symptoms.—There has been much painstaking study of the effect of the smoking of tobacco upon the intellectual, moral and psychic functioning of the human mechanism. It has been deliberately stated by investigators whose reputation for accurate and painstaking research demands that attention be given to their opinions, that the intellectual capabilities of students are dulled by the immoderate use of tobacco. A study of the effect of chronic nicotinism in laborers in industry, whose output could be measured in day units, has led others to contend that smoking and chewing tobacco lower the output rate in strenuous physical trades, particularly in the later hours of the day, the heavy smokers showing less ability than the light smokers or abstainers to respond to the increasing pressure of the late afternoon hours. J. R. Earp is responsible for the statement that, in Antioch College, the 47 per cent of the students who did not use tobacco excelled in athletics and scholarship. Other authorities have been unable to confirm the general application of this statement.

Whether the disregard for the rights and comfort of others, manifested by some smokers, is a sign of ethical deterioration must be left to the individual reader to decide.

In the study of the symptomatology of nicotinism one encounters very largely a subjective rather than an objective picture. To be sure, the mucosa of the nasopharynx is sometimes seen to be irritated and reddened, and at times a rather extensive catarrhal affection of these tissues may extend to adjacent structures, blunting the sense of taste, smell and even

hearing. A most interesting symptomatology, however, is associated with the cardiovascular system. Moschcowitz has described the occurrence of cardiac arrhythmia of various types, extending even to delirium cordis. The angina described by Allbutt is of extreme severity, and of prolonged duration. The latter quality differentiates it from true angina pectoris. Blood-pressure is said to rise during smoking, and to fall below the normal level after cessation.

There are two types of precordial distress, which have been ascribed to the effect of nicotin. The first has been mentioned. The second consists of what may be termed substernal or precordial tension. They are without definiteness in onset, and with no reference of pain. John, Wilson, Favaher, Neuhoff, Cushny and others have described a variety of symptoms, referable to the cardiac apparatus, which include bradycardia, tachycardia, precordial weight (heart consciousness), cyanosis, and even Cheyne-Stokes' respiration, auricular flutter, and extrasystoles have been known to follow the excessive consumption of tobacco. Cushny explains that these symptoms may be due to a displaced cardiac rhythm, mainly as a result of a neuropathic influence upon the terminations of the vagus, and sympathetic nerves. Hence, slowing and acceleration, dependent upon which action predominates, might be seen.

Gallavardin studied 200 male patients, suffering with angina pectoris, with no sign of lues. Twenty-seven per cent had never smoked, and, in addition, 4 per cent had given up smoking before the first attack of angina; 18 per cent were immoderate, and 38 per cent were mild smokers. This observer contends that in at least 50 per cent of this series tobacco cannot be placed as a definite cause. Parkinson and Koefed, in a study of thirty smokers, ascribed breathlessness, and the so-called effort syndrome, to the inordinate use of tobacco. The average pulse rate, in this series, was nine beats per minute higher during smoking.

It has been stated that nicotin produces depression of the vagus, and, as a consequence, acceleration of the pulse. The vasomotor irritability resulting produces an irregular blood supply to the brain and other organs, and a sensation of irritability and depression, with periods of shortness of breath on exertion, giddiness and palpitation. This syndrome, including cardiac irritability, precordial pain and anxiety, with syncopal attacks, has been termed vagatonia. The pain associated with this condition may take the form of sharp, sticking sensations in the precordium, or of a dull ache over this area, or in the throat. It will be noted that these subjective symptoms are found in those areas supplied by the pneumogastric nerve.

The respiratory rate was unaffected, and the systolic blood-pressure was raised from 5 to 10 millimeters of mercury. Dixon reports two thousand psychological tests on medical students. As a result of this study, he believes that smoking lowers the mental efficiency from 10 to 23 per

cent, particularly in the perception and association of ideas. In military campaigns, it has been felt that the use of tobacco enables the soldier to endure hardships and hunger, and that inhibited hunger contractions made forced marches, without food, possible.

As has been intimated above, symptoms referable to the cardiovascular system stand out rather conspicuously in the picture of chronic nicotin poisoning. It is interesting to note that many of these signs are strongly subjective, and assuming, as they do, a neuropathic aspect, ofttimes physical examination fails to reveal substantiating objective findings.

It has been asserted by Blanc that tobacco is incapable of producing atheroma of the vessels, or serious lesions of the myocardium. This same observer states, without qualification, that nicotin does not seriously damage the heart or blood-vessels unless some organic lesion is present. Blanc, however, concludes that tobacco should be forbidden men of advanced age when cardiovascular lesions are suspected.

Brigham, Kerr and others describe serious myocardial damage, and the occurrence of other cardiac and vascular ailments common in middle or advanced life, to the immoderate use of tobacco.

There seems to be but little doubt that in well-controlled experiments there has been observed a rise in blood-pressure and pulse rate, which could be definitely ascribed to nicotin poisoning, and it is safe to conclude that precordial pain, or at least a feeling of weight in that region, is produced by excessive smoking. As a proof of the causative factor in this condition, it has been repeatedly observed that these symptoms rather promptly disappear upon the termination of the habit of smoking.

As far as the gastro-intestinal symptoms are concerned, the literature contains fewer findings as to the production of harmful results from the use of tobacco. Adler believes that excessive cigarette smoking results in the production of symptoms resembling those of peptic ulcer. The gastric acidity, however, is only slightly increased, but an accelerated peristaltic movement is discovered in these patients. A tendency to gastric spasm is not unusual.

Ortner has described a syndrome, which he terms intermittent arteriosclerotic dyspepsia, and which he ascribes to the inordinate use of tobacco. Meteorism, fetid stools, alternating diarrhea and constipation, spasms of the sphincter-ani muscle, and subsequent hemorrhoidal disturbances are considered by this observer as being due to chronic nicotinism.

Oncologists have repeatedly called attention to the fact that chronic irritation of the mucous membrane of the lips and mouth may play a part in the production of malignancies of these structures.

Some interesting special sense symptoms have been observed in the habitual smoker. Dixon, in 1927, reported that the literature revealed forty-eight cases of tobacco amblyopia. Von Frankel-Hochwart, in 1923, stated that nicotin poisoning may cause impairment of hearing, deafness,

vertigo, dizziness, and other symptoms pointing to disturbed vestibular function. De Schweinitz has observed what he believes to be a true case of tobacco amblyopia, and Hart, in 1925, reported ten cases of bilateral neuritis of the eighth (auditory) nerve, which he deemed due to nicotin. The occurrence of certain neuralgic symptoms, as well as of sudden sharp pain in the interior of the skull, has been mentioned by reliable clinicians as being produced by nicotinism. Finally, Terson states that in these cases vision improves as evening approaches. There is a central scotoma, and color-blindness for small patches of color is observed.

There has been much discussion as to the relationship of the incidence of tuberculosis to the habit of smoking. There are those who believe that infection of the lungs with the tubercle bacilli is favored by the excessive, or even moderate, use of tobacco. Fishberg states that smoking has no effect on a tuberculous process in the lungs. Krause does not consider that chronic inflammatory conditions predispose to bacteriological infection; while Webb, from a study among soldiers, concludes that smoking does not predispose to tuberculosis. Not a few reputable observers concur in this statement, and some even advise permitting tuberculous patients to smoke, provided there is no throat condition present. There are a number of equally reliable physicians who strenuously oppose this policy. Since nicotin is a rather active vasoconstrictor, it would seem unwise to permit patients with any pulmonary pathology which might predispose to hemorrhage, to smoke.

Some interesting studies have been made in regard to the industrial hazard involved in the manufacture of cigars and cigarettes. Kober and Hanson, a decade ago, stated that 42 per cent of those engaged in this industry were females, and that 3.9 per cent were children under sixteen years of age. Eighteen per cent of these were concerned in the manufacture of cigars and cigarettes. (It may be remarked here in passing that the adoption of machinery in the manufacture of cigars has made unnecessary the unsanitary practice of using saliva to seal them, and has removed in this way not only a disease hazard to the worker, but to the consumer as well.)

As to the incidence of tuberculosis among this great group of persons employed in the tobacco industry, Roth studied Austrian statistics, covering 35,000 tobacco workers. This observer showed that among the causes of death in this group, tuberculosis occupied first place. Two decades ago, the United States Census Bureau announced that among twenty-three occupations tabulated, tobacco workers occupied second place in the mortality from tuberculosis, marble and stonecutters only exceeding them.

As to the local effects of nicotin on workers in this industry, it has been found that the dust in the above establishments, manufacturing cigars and cigarettes, contains 0.56 per cent of nicotin. Kostial has shown that 72 out of 100 females, employed in a Vienna cigar factory suffered from

congestive headache, palpitation of the heart, inhibition of the pulse rate, cardiac consciousness, gastralgia, pyrosis, vomiting, diarrhea, insomnia, anorexia and general fatigability.

Kostial remarks the similarity between these symptoms and those produced in animal experimentation.

It is interesting to note, as explanatory of the relatively low incidence of serious chronic nicotin poisoning, that while the amount of nicotin in different kinds of tobacco varies, as has been stated above, from 1 to 8 per cent, at least one-half of this alkaloid is destroyed by combustion, while the other half can be isolated from the smoke. Nicotin displays somewhat of a cumulative action, being excreted more slowly by the urine than it is absorbed, in the case of excessive smokers.

Finally, there appears to be no satisfactory explanation as to the pleasurable effects secured by the blood absorption of nicotin. Sir Lauder Brunton believed that the regularity of pulling on the pipe caused a rhythm in the respiratory rate, which is reflected in other organs, giving a sensation of calm. It has been suggested that in small doses nicotin may mildly stimulate nerve-centers and produce an exhilarating effect.

Diagnostic Possibilities.—Symptoms referable to the cardiovascular system may bring about a confusion in the mind of the physician as to whether actual myocardial disease exists, or whether the symptoms are due to chronic nicotin intoxication. Peptic or duodenal ulcer must be differentiated from nicotin poisoning, and the blindness sometimes seen as a result of the toxic ingestion of nicotin must be differentiated from that produced by alcohol, lues, or an optic neuritis, due to one of several other causes. Fatigability, loss of weight and similar evidences of poisoning may be mistaken for pulmonary tuberculosis.

Diagnosis.—In taking the history of a patient, the physician usually inquires about the patient's personal habits. The amount of alcohol consumed, tobacco used, kind and amount of food eaten, and hours of sleep, are usually included in this inquiry.

In cardiovascular disease, the symptoms of this condition and of chronic nicotinism may be difficult to differentiate. On the other hand, the presence of palpitation, dyspnea, precordial pain, or anxiety, with no definite evidence of cardiac or vascular pathology discernible on physical examination, and with a history of excessive smoking, would naturally incline the physician's opinion toward nicotin poisoning. At times, distress or pain over the aortic region suggests the presence of an aortitis. Of the greatest importance, however, in confirming the diagnosis of chronic nicotin poisoning is the rather prompt relief of symptoms, which results when the patient refrains from smoking. This fact has ofttimes been useful in bringing about a correct diagnosis. The relief of symptoms, referable not only to the cardiovascular system, but to the gastro-intestinal and special-sense systems, follows the termination or reduction of the toxemia.

The symptoms of chronic nicotinism are ofttimes mistaken for those produced by peptic or duodenal ulcer. In the former instance, however, the gastric acidity is but slightly increased, and the occurrence of pain is not so closely associated with the consumption of food. If the patient is an immoderate smoker of tobacco, interdiction in its use will relieve the symptoms.

In eye conditions, presenting diplopia or complete blindness, the diagnosis is not always easy. In the presence of the history of excessive smoking, or the working with tobacco in the cigar and cigarette manufacturing industry, toxic nicotinism should be suspected. When a patient is removed from contact with tobacco and the eye symptoms improve, the diagnosis is thereby clinched.

Prognosis.—Most observers contend that no permanent damage is usually done by the chronic absorption of nicotin, particularly if the patient can be brought to cease the use of tobacco. In the presence of a definite arteriosclerosis, as a result of a persistently elevated blood-pressure, or of a toxemia from nicotin, irremediable damage to the cardiovascular system may be sustained. Toxic eye conditions and gastro-intestinal dysfunction are quickly relieved by the withdrawal of the drug.

The prognosis in chronic nicotin poisoning may, therefore, be said to be as favorable as the patient is sensible and the doctor discerning.

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POISONING FROM THE USE OF COSMETICS

Introduction.—A half century ago an English writer, in describing the origin of the urge for personal adornment, remarked the fact that the flowers plucked from the bush, the scarlet berries of the shrub or tree and the delicately tinted shells of the river banks or lake shores were the only adornments of the early woman of the world. The only cosmetic which tinted her lips and cheeks was the harmless sunshine. Then man strove to so alter his natural countenance as to arouse a feeling of awe or fear in those who gazed upon his face. Then war was his business and it was his intention to so distort his visage that enemies would flee on beholding him and friends would be moved to admiration because of the originality, the absurdity and the fearsomeness of his facial transformation.

In these jolly days of jazz, the picture seems to have been reversed and it is the woman who apparently is endeavoring to usurp original man's prerogatives. In the days of our grandmother, the vermilion of lips, the rosy tint of cheeks bespoke corpuscles rich in hemoglobin. Good food, long restful hours of sleep, diversion which entertained but did not take its usurious toll of health and strength, play and work in sunlit rooms, exercise under the dome of the great outdoors were cosmetics possessed of great potency and had no damaging tendencies to health. But, alas! while these remedies are still to be procured by the hardy, cosmetics which fail to beautify and which often contain ingredients actually injurious to the human body, both locally and systemically, are for sale everywhere. It is surprising to note that in a recent year the sum of nine million four

hundred and eighty thousand dollars was spent for hair tonics and one million seven hundred and fifty thousand dollars for hair dyes.

Cosmetics may be defined as external applications intended to beautify the complexion, skin or hair. Specifically they include hair oils, dyes, bleaches, tonics, shampoos, facial creams, powders and rouge. To this general list may be added for the sake of completeness, depilatories, deodorants, grease paints as well as not a few miscellaneous preparations with uses allied in purpose to those mentioned above. While many of these preparations possess neither virtue nor harm, yet not a few are capable of producing poisoning in the user because of the absorption of the dangerous substances which they contain.

If the recognition and treatment of toxicoses due to the ingestion of poisons through the use of such preparations could be assured by omitting mention of specific examples of such offending nostrums, this policy would be followed. But such does not seem to be possible, and hence generality must give way to specificity in discussing poisoning as a result of the use of cosmetic preparations.

There are various combinations of drugs which for decades have had some vogue among those who have felt the need for personal beautification. Hair dyes are expected to supply all colors from a youthful black to a middle-aged henna. Each of these colors is secured from either the use of a single dominant drug or a combination of such agents. And yet it is interesting to note that chemical analyses reveal but a comparatively small number of drugs which are more or less standard ingredients of such cosmetics as hair dyes, facial bleaches, freckle removers, shampoos, depilatories or rouge. While many of these preparations purport to bring about unbelievable changes in facial appearances and almost as regularly fail to justify these claims and hence are fraudulently sold, this type of cosmetic is comparatively harmless when compared with others which contain vegetable or mineral poisons. However, McCafferty states that vegetable hair-preparations are much less likely to do harm than those whose *active ingredients* are derived from the mineral kingdom. Synthetic organic dyes are almost sure to contain paraphenylendiamin.

The following general statements may be useful relative to the chemical composition of the common types of cosmetics:

1. Anti-freckle lotions, facial bleaches and similar preparations are very apt to contain some form of mercury, either as the bichlorid or in its ammoniated state. These are, of course, capable of doing much harm.

2. Hair dyes commonly contain lead in the form of the acetate which with sulphur in suspension forms a lead sulphid intended to impart a brown color to the hair. Black dyes often contain the dangerous paraphenylendiamin. This drug has been responsible for a number of cases of poisonings as a result of the use of black hair dye. In addition, silver nitrate is responsible for the action of not a few dyes. Several of the

so-called walnut dyes contain this drug. Henna dyes frequently contain paraphenylendiamin. Methyl alcohol in as great concentration as 42 per cent has been used as a solvent in these dyes. The possibility of harm from this ingredient is patent to all.

3. Dandruff removers are quite apt to contain arsenic together with salicylic acid and such relatively harmless ingredients as resorcin, balsam of Peru and sulphur.

Nor is poisoning following the use of a cosmetic containing a poisonous drug at all rare. In 1925, due to the frequency of toxicoses from this source, the Chairman of the Section on Dermatology and Syphilology of the American Medical Association appointed a committee under the chairmanship of H. N. Cole to study this matter and report its findings together with suggested remedies. Discouraging though it was to receive but sixty replies to a questionnaire 437 copies of which were sent to the leading dermatologists of the country, much useful information was secured. This investigation disclosed the fact that forty-three poisonings had occurred from the use of rouge, bleaches, grease paints, face powders and creams. Thirty physicians reported toxicoses from the use of hair tonics and shampoos containing poisonous substances. Seventy-four poisonings of various grades directly traceable to the use of hair dyes were reported. Hence the possibility of an unexplained symptom picture being due to the employment of cosmetics should be continually borne in mind by the physician, since drug toxicoses of this type remain too often unrecognized. Recently, in an eastern hospital, a patient was treated for neuritis which was thought to be due to some form of focal infection. After a careful study by competent clinicians it was decided that the source of the difficulty was in the teeth, a number of which were extracted. The pain persisting, however, it was accidentally learned that the patient had frequently purchased a face powder containing white lead from a nearby drugstore. As a result of this discovery, the case was finally diagnosed as one of lead poisoning. The substitution of starch for white lead worked a cure.

It would seem appropriate at this juncture to be somewhat more specific in describing the type of preparations from which poisonings may result.

Facial Bleaches and Freckle Removers.—The percentage of mercury found in facial bleaches may vary from 1.5 per cent to 12 per cent. It has been stated [1] that the following preparations are dangerous because of the fact that they may subject their users to mercury toxicoses:

Anti-Freckle Lotion contains 1.5 per cent of bichlorid of mercury.
Mrs. Bradley's Face Bleach contains 23.6 per cent of mercuric chlorid.
Freckle-eater contains 4 per cent of ammoniated mercury.
Freckleless contains 12 per cent of ammoniated mercury.

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[1] *Nostrums and Quackery*, Chicago, American Medical Association, 1921, Vol. II.

> Kingsbery's Freckle Lotion contains 0.5 per cent of bichlorid of mercury.
>
> Othine contains 11.5 per cent of ammoniated mercury.
>
> Dr. Palmer's Skin Whitener contains 7.8 per cent of ammoniated mercury.
>
> Perry's Freckle Lotion contains 1.6 per cent of mercuric chlorid.
>
> Tan-a-Zin, Stillman's Freckle Cream and many others contain either bichlorid of mercury or mercury in ammoniated form.

With mercury in the above concentration and recognizing the fact that poisonings may take place as a result of absorption through the skin, it should not be at all surprising for the physician to encounter such symptoms of mercury poisoning as pyorrhea, diarrhea, intestinal cramps, malnutrition with marked loss of weight and evidences of a more or less severe grade of nephritis. The diagnosis of mercury poisoning, chronic in type, which would result from an ingestion of small quantities of this poison covering a long period of time, might be missed unless the frequency of its use in facial bleaches is remembered. It is only necessary, therefore, for the physician to recall the possibility of this type of poisoning in order to arrive promptly at the proper diagnosis and treatment.

Hair Dyes.—Poisoning as the result of the ingestion of lead is one of the chief dangers in the use of hair dyes. To be sure, there are other ingredients employed for this purpose, but it is well for the physician to remember the frequency with which lead is found in these preparations. A distinguished citizen of an eastern metropolis is said to have lost his sight as a result of a lead neuritis due to the use of a plumbum containing hair dye. The concentration of this agent in some dyes is only explained by the stupidity and pharmacologic ignorance of their originators. One well-known dye contains 23 per cent of lead acetate together with Glauber salts and calcium chlorid. In another, chemical analysis reveals the presence of iron, copper chlorid and pyrogallol. The following preparations are reported [2] by chemists as containing lead: Allen's Hair Color Restorer, Barbo Comp, Natholina, Parker's Hair Balsam, Phoenix Seminole Hair Restorer, Q-Ban Hair Color Restorer, Swissco, Manhato.

A number of cases of poisoning have resulted from the use of Simplex Hair Coloring, according to the McClure-Westfield Laboratory. This preparation contains paraphenylendiamin.

In another so-called color restorer 1.68 grams of lead acetate per 100 c.c. of solution was isolated by the official chemists of an eastern state. One case of plumbic neuritis and two of dermatitis of the forehead and neck have been definitely traced to the use of this preparation. A case of argyria has been reported following the use of a hair restorer containing silver nitrate. Some type of oxidizing agent is commonly employed in prep-

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[2] *Ibid.*

arations intended to bleach the hair. A nostrum, L'Areal Henna, for example, is said to contain sodium perborate, iron, copper, pyrogallol, together with some vegetable matter.

Depilatories.—Most of these preparations depend on barium sulphid or barium sulphate. A popular article contains 14 per cent each of barium sulphid and barium sulphate with a lesser quantity of sodium sulphid. Another contains iron and dilute hydrochloric acid, while a third derives its potency from the sulphid of arsenic of which it contains 23.5 per cent.

The harm which such preparations might do in the hands of the ignorant and careless can be more than surmised. It would appear unnecessary and indeed impossible to attempt to further enumerate members of the cosmetic group of preparations capable of working harm to those using them. When symptoms of lead, arsenic, silver, anilin, mercury or other drug toxicoses are present, a suspicion of cosmetic poisoning should be aroused. The reader is referred to a discussion of the symptomatology, diagnosis and treatment of these poisonings fully detailed elsewhere in this work. The prevention of such conditions is, of course, of prime importance. Until unscrupulous men and women, however, are no longer avid for money gained by questionable means and until persons of all ages and both sexes are willing to patiently bear the imperfections in form and color which nature bestowed upon them, physicians will still be asked to relieve those unpleasant symptoms which follow in the footsteps of folly.

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CHAPTER XXVIII

RADIO-ACTIVE SUBSTANCES

J. F. ROGERS

Radio-active substances, almost since their discovery, have been recognized as possessing potent powers for ill as well as for good, and within the past two years it has become evident that they may prove a serious menace to those who help to produce them or who handle them in their daily work.

Occupations.—The chief occupation in which radio-active substances are used is that of painting the hands of timepieces. For this purpose, radium, mesothorium and radiothorium are used, but chiefly the two latter because of their greater luminosity. Unfortunately, these have the strongest physiological influence of the group. The radio-active material is mixed in very small quantity with crystalline zinc or zinc sulphid, and the mixture is made into paint in quantities and of a consistence needed for immediate use by adding an adhesive substance and water. The paint so prepared is applied with a small camel's hair brush, and it has been the practice of the girls employed in this work to point the brush by drawing it between the lips. Not only does the radio-active material come in contact with the body during this procedure, but, as observed by Flinn, in the process of mixing the paint, drops are often splashed on the hands and the substance is conveyed in turn to the face, hair and clothing. Cloths are used for wiping and drying the brushes and the material also reaches the aprons worn which show its presence even after being laundered. The radio-active substances must, in such an occupation and with such practices, be taken into the body by the digestive and respiratory tracts, and if not absorbed through the skin, some effect might be expected from the materials deposited on the skin.

Pathology and Symptoms.—In experimental animals no local effects were produced by prolonged painting of the skin and mucous membrane of the mouth with the luminous material, and in feeding experiments 98 per cent of the radio-active materials were excreted within a few days after the exposure had ceased. However, radium is deposited in the bones of such animals and it is stated by some investigators that when so deposited in insoluble form, there is no known way of changing or eliminating it, save the very slow one of radiation.

As might be expected from these experiments, and the known potency

and danger of such substances in therapeutics, the chief manifestation of occupational disease has been on bone and on the blood-forming mechanisms. The former, being the more striking and evident to gross observation, has most attracted attention to the disease, though disturbance of blood-formation comes much earlier and is far more universal.

Manifest disease in bone has been comparatively rare and has exhibited itself chiefly in the mandible in the form of a necrosis resembling the phossy jaw of cursed memory. Destructive lesions in other bones are said to have been demonstrated by roentgenograms (Martland) especially in those bones subject to injury, as in the feet, or in those carrying considerable weight, as the heads of the femurs. Lesions of the liver and spleen, seemingly identical with those of ordinary leukemia, have also been reported.

Amundsen states that the blood-picture of persons working with, or in the immediate vicinity of, radium always shows deviation from the normal. The absolute number of white blood-cells is often less than usual, but the most marked change is in the ratio of the polymorphonuclear leukocytes and the lymphocytes, the former being reduced and the latter increased. The red blood-corpuscles are often abnormal. The hemoglobin usually remains normal. Amundsen states that these effects are apparent after two months' exposure and even in maid servants working in the laboratory.

Castle, Drinker and Drinker give the following average blood-pictures for twenty-two radium workers, fourteen of them with extensive exposures:

Blood-Conditions		Radium Workers, Per Cent	Normal, Per Cent
Red blood-cells	below 4,000,000	6	0
	between 4,000,000 and 6,000,000.	75	100
	above 6,000,000	19	0
White blood-cells below 7,000		27	0
Polymorphs	60 to 70 per cent	55	100
	below 60 per cent	45	0
	below 55 per cent	32	0
Lymphocytes	between 20 to 25 per cent	18	100
	above 25 per cent	64	0
	above 35 per cent	27	0
Mononuclears	between 3 to 8 per cent	41	100
	above 8 per cent	59	0
Abnormal red cells		36	0
Without blood-abnormalities		0	100

Allowance must be made as regards the total number of both erythrocytes and leukocytes to the usual effects of indoor, sedentary occupation.

A low blood-pressure is common among workers affected by radium

and, as might be expected, weakness is likely to be the earliest and most frequent symptom. Disturbance of menstruation is reported and sterility may result.

Diagnosis.—The fact that the symptoms are not at all distinctive renders the importance of occupational history most apparent; aside from this the careful examination of the blood is very important. Necrosis of the jaw would, of course, render the clinician suspicious. Radio-activity in the body is said to be best detected instrumentally in the expired air but such examinations should be made by a physicist versed in radium work.

Prevention and Treatment.—From our present knowledge, work with radium, in the minute quantities ordinarily used in industry, seems not likely to produce serious results if the material is not taken into the body. It is recommended that the mixing of radio-active paints be carried on in rooms separate from the usual work room and that the material be handled under a hood with rubber-gloved hands. Rubber gloves should be worn at work, and long-sleeved, high-necked aprons which are washed weekly. If gloves are not worn, care should be taken to keep the hands from the mouth or other part of the body and they should be thoroughly washed before meals and after work. Workers' desks should be covered with sheets of paper to catch paint, and these sheets should be burned each day at the close of work. The mouthing of paint brushes should be prohibited. There should be ample washing facilities with individual soap and brush and paper towels. The work room and wash room should be scrubbed throughout every month, and the equipment kept thoroughly clean. There should be no dry cleaning. The work room should not be used as a lunch room.

All workers should be constantly under medical and dental supervision. Blood examinations should be made at least every month and workers who seem especially susceptible should be excluded.

It has been recommended that the work day should not be over seven hours and that, besides Sunday, two half-holidays a week should be allowed. There should also be a semiannual vacation of two weeks. When symptoms or signs of poisoning occur the worker should be given a vacation until he returns to normal.

Since fatalities which could possibly be attributed to occupation have been very few, compared to the number of workers, it would seem that with proper supervision their risk is slight, unless it be that a few are especially susceptible. Martland states, however, that, even with the most modern methods of protection, all workers with X-rays and radio-active substances "are potential candidates at any time for the development of a serious and fatal anemia or leukemia." Where radio-active materials are produced or handled in quantity, special precautions should be taken to prevent undue exposure, by the use of leaden shields and lead glass, as is the case in the handling of X-ray machines. Such materials should not be

stored in the neighborhood of workers and should be encased in suitable lead-covered receptacles.

There is no specific treatment for persons affected by these substances other than removal from work and the practice of good hygiene.

CHAPTER XXIX

TREATMENT OF ACIDOSIS AND ALKALOSIS

James L. Gamble and Kenneth D. Blackfan

INTRODUCTION

The terms acidosis and alkalosis describe deviations of body fluid reaction from the normal value. These disturbances of reaction are an incidental result of various abnormal processes, but may be of such degree as to urgently require directly corrective measures, pending the outcome of treatment of the underlying disease. The circumstances which lead to acidosis or to alkalosis are numerous and they produce diverse distortions of the chemical anatomy of the body fluids. In a given clinical situation, correct choice of therapeutic agents depends on an understanding of the structural defect in the body fluids which is responsible for the change of reaction. For this reason, the following presentation of pathogenesis is considered necessary as a basis for discussion of therapeutic measures.

PATHOGENESIS

The reaction of the blood-plasma is determined by the ratio of the concentrations of two substances which exert opposing effects: the weakly acid substance, carbonic acid, and its alkaline salt, bicarbonate.[1] The normal reaction of the plasma is the result of closely stationary concentrations of these substances; the average value for carbonic acid being 3 volumes per cent and for bicarbonate 60 volumes per cent. A change from the normal value for either factor will cause a change in the reaction of the plasma. The concentration of carbonic acid in the plasma is determined by the carbon dioxid content of the residual air in the lungs and this in turn depends on the rate and volume of lung ventilation. The carbonic acid factor is thus controlled by the respiratory mechanism, and

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[1] Data regarding changes of reaction in the body fluids have necessarily been derived chiefly from the blood-plasma. We may reasonably assume that a change found in the plasma extends, at least in some degree, throughout the body fluids.

With the purpose of simplifying discussion, the presence in the plasma of the acid and alkaline salts of phosphoric acid is here ignored. Further justification for this omission is that, although these substances play an important rôle in regulating the acidity of the urine, they are not direct factors in the control of plasma reaction, since here the ratio of their concentrations *follows* the reaction established by the carbonic acid: bicarbonate ratio.

so dependable is this control that a disturbance of body fluid reaction is almost never referable to an incorrect concentration of carbonic acid.[2] It follows that deviation of the plasma reaction from its normal value is practically always the result of change in the other control factor, bicarbonate concentration. Decrease of bicarbonate causes an abnormal degree of acidity (acidosis), and increase an unusual alkalinity (alkalosis). A description of the pathogenesis of these conditions consists in an explanation of the change in bicarbonate. An obvious first requirement here is an understanding of those factors of plasma structure which determine the size of the bicarbonate concentration and which normally sustain a closely stationary value.

The relationships of the bicarbonate concentration to other parts of the chemical anatomy of the blood-plasma can be briefly described with the help of the diagram in Figure 1. The left-hand column represents the fixed base concentration, which is composed of magnesium, calcium, potassium and sodium, the last being by far the largest factor. In the other column are the acid factors which together cover the plasma base. The plasma proteins behave as acid substances, and their base equivalence is indicated in the diagram. The organic acid factor is composed of the radicals of organic acids derived from the metabolism of protein. It will be noted that the largest acid factor is chloridion, the radicals of sulphuric acid and of phosphoric acid being conveyed at relatively small concentrations. The concentration of bicarbonate ion completes the column. The line down the center of the diagram represents an important fact; namely, that the so-called salts of the plasma are practically entirely dissociated into their component ions. Another fact, still more important to keep in mind, is that the factors indicated in the diagram may vary individually. For instance, as will presently be shown, an increase or decrease in the concentration of chloridion may occur without corresponding change in the concentration of sodium. Obviously, then, our
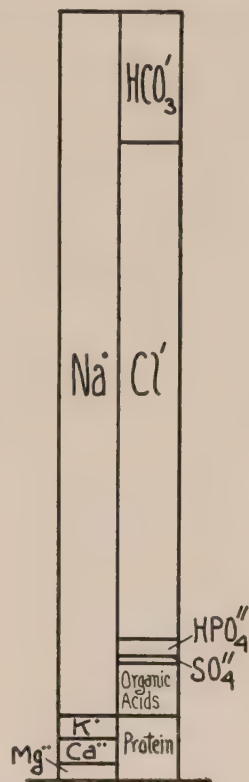
Fig. 1.—The Acid-Base Composition of Normal Blood-Plasma.

The data used in constructing the diagram were the average normal values for the individual factors expressed as c.c. 0.1 or per 100 c.c. The values for the bases are superimposed in the left hand, and those for the several acid radicals in the right hand column.

[2] It is of course possible that intracranial lesions may affect the respiratory center and cause acidosis or alkalosis by disturbing respiratory control of the carbonic acid concentration in the plasma, but actually this happens extremely rarely.

habit of thinking of the inorganic substances in the plasma as salts is incorrect, since we have to deal with separately controlled concentrations of ions. The one all important requirement in the acid-base structure of the plasma is that the sum of the concentrations of the acid radicals be kept exactly equal to the plasma content of fixed base. This arrangement of exact acid-base equivalence, which the diagram describes, is obtained by adjustment of the bicarbonate ion concentrations.[3] To briefly illustrate and explain the unique adjustability of the bicarbonate factor, let us suppose that abnormal circumstances have caused a change in the chloridion concentration. An increase of chloridion will dispossess an equivalent amount of bicarbonate ion of base by reason of the fact that it is the radical of a much stronger acid. This is also true for all of the other acid factors in the plasma. The released bicarbonate ion becomes carbonic acid, and this is rapidly removed by way of the lungs, so that only momentarily does this event cause an increase of free carbonic acid in the plasma over the normal level. On the other hand, a reduction of the chloridion concentration will tend to expose fixed base. This is prevented by replacement of chloridion by bicarbonate ion, derived from the carbonic acid concentration which the respiratory mechanism sustains in the plasma. The chief physiological purpose of the presence of bicarbonate in the plasma is to maintain by its automatic adjustability the balance of acid and basic ions which the diagram represents. Obviously, since bicarbonate is one of the two factors controlling reaction, any defect in plasma structure which makes necessary a considerable adjustment of bicarbonate will be accompanied by a change of reaction. The extent of this change of reaction is, however, almost infinitely less than would be caused by the exposure of strong base or of strong acid, which the bicarbonate adjustment prevents. The enormous limitation of the change in reaction thus obtained is often described as the "buffer effect" of bicarbonate.[4]

It is hoped that the above discussion has made clear the fact that

[3] It should not be inferred that the equivalence of the concentrations of anions and cations which the diagram represents provides neutrality of reaction. To such extent as fixed base is covered by the radical of the weak acid, carbonic acid, the alkaline substance bicarbonate is present. The remainder of the diagram being composed of strong base covered by the radicals of strong acids may be taken to represent neutral substances.

[4] Here we must remember that change in size of the bicarbonate concentration may be compensated for to a certain extent as regards effect on reaction by respiratory adjustment of the other factor controlling reaction—namely, free carbonic acid. For instance, if the plasma bicarbonate be lowered, the reaction of the plasma will change in the direction of acidity. Theoretically, this change can be prevented by a corresponding reduction of the free carbonic acid in the plasma. In the presence of a lowered bicarbonate the respiratory mechanism usually does undertake to lower the free carbonic acid in the plasma. This attempt at compensation gives us our one clinical sign of acidosis, which we call *hyperpnea*. Compensation by respiratory adjustment of free carbonic acid is, however, never more than partial; so that whenever we find any considerable

a change in bicarbonate is not a primary event, but is always the result of a change in some other factor or factors in the acid-base structure of the plasma. It is, therefore, evident that therapeutic measures cannot be correctly devised without knowledge of the underlying defect. Such knowledge can only be gained by bringing into view all or, at least, the chief factors of plasma structure. The diagrams in Figure 2 are presented for the purpose of describing by means of actual examples the changes in the acid-base structure of the plasma found in the presence of various abnormal circumstances. The diagrams are constructed from direct measurements of the chief structural factors; namely, total fixed base ($B^{\cdot}$), chloridion (Cl') and bicarbonate ion (HCO'_3). The smaller acid factors (see Fig. 1) were not individually measured. Their sum is measured by the remainder of base uncovered by chloridion plus bicarbonate ion, and is designated R' in the diagrams. For comparison the values for normal plasma are presented in the first diagram. The remaining diagrams explain abnormal values for bicarbonate in terms of changes found in other factors. They need, therefore, be only briefly discussed with mention of the clinical circumstances behind them.

Diagram 1 represents data obtained from the blood-plasma of a patient with a cancer of the pylorus which had rather suddenly produced an almost complete obstruction. Before entering the hospital the patient had for several days vomited stomach secretions almost continuously. The diagram at once indicates the cause of the huge concentration of bicarbonate ion; the concentration of chloridion which is normally the chief acid factor in the plasma has been reduced to about one-third of its usual value. The alkalosis of upper intestinal obstruction is thus easily understandable as a necessary extension of bicarbonate in replacement of chloridion lost in vomited stomach secretions. It may also be learned from the diagram that, large as the bicarbonate value actually is, its extension has been greatly limited by two other changes; an appreciable loss of fixed base from the plasma and a large increase in the value for R', the later change being probably in large part due to concentration of plasma proteins as a result of the extensive dehydration of the plasma which always accompanies continued loss of stomach secretion.

Diagram 2 presents measurements from the blood-plasma of an infant suffering severely from infectious diarrhea (dysentery). This infant did not vomit. The changes found in the plasma are the result of loss in diarrheal stools of materials drawn from the blood-plasma for construction of digestive secretions entering the intestine. Agreeing with our knowledge of the composition of these secretions we note in the diagram a relatively larger withdrawal of fixed base than of chloridion, with the

reduction of the plasma bicarbonate we know that the reaction of the plasma has actually to some extent changed in the direction of acidity and we can correctly describe the situation as acidosis.
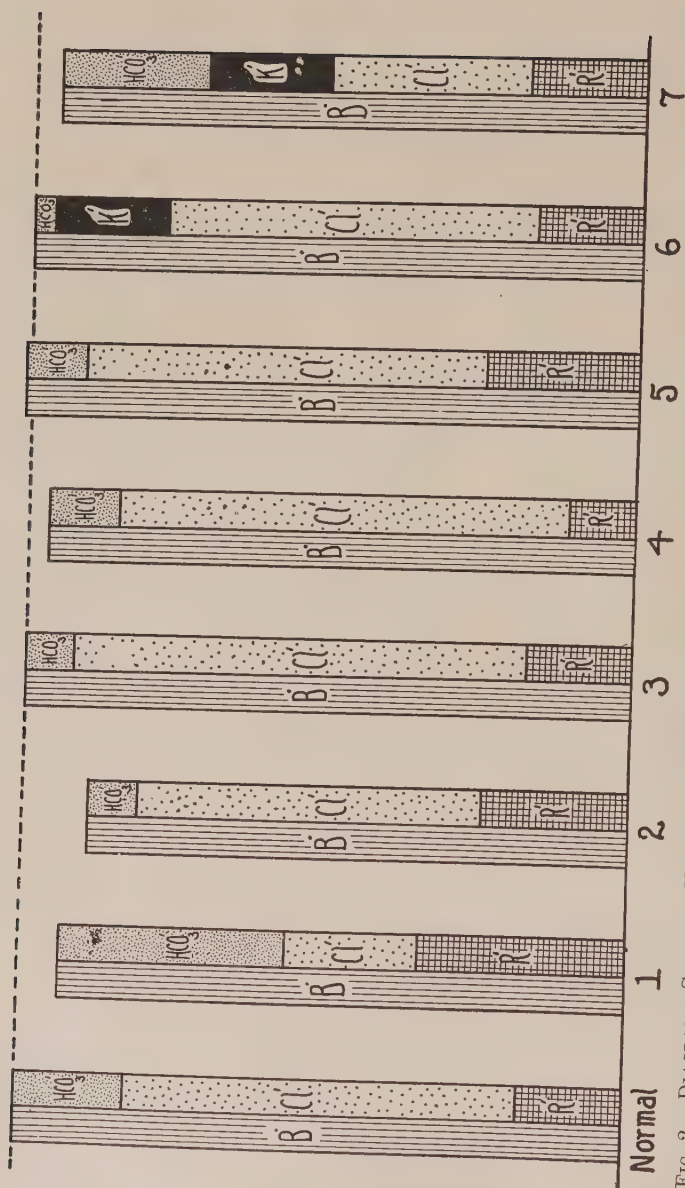
Fig. 2.—Diagrams Showing Various Defects in Acid-Base Structure of the Blood-Plasma and the Necessary Change in Bicarbonate.

No. 1, Alkalosis of pyloric obstruction. No. 2, Acidosis caused by diarrhea. No. 3, Calcium chlorid acidosis. No. 4, Chlorid acidosis in tubular nephritis. No. 5, Retention acidosis in glomerular nephritis. No. 6, Acidosis due to ketosis; diabetes. No. 7, Alkalosis in the presence of ketosis; upper intestinal obstruction.

The diagrams are constructed from direct measurements of total fixed base (B'), chloridion (Cl') and bicarbonate ion (HCO'₃). The smaller acid factors (see Fig. 1) were not individually measured; they are contained in the remainder (R').

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result that much less than the usual amount of base is present as bicarbonate. An additional factor in the reduction of bicarbonate is a considerable extension of the value for R′.

Diagram 3 describes the production of an acidosis for a therapeutic purpose by administration of a so-called acid-producing salt. The measurements here used are from an infant with tetany receiving calcium chlorid by mouth. The reduction of bicarbonate is due to a single change: a large extension of the concentration of chloridion. The explanation of this change is that the ingested calcium almost entirely escapes absorption and, bound by fatty acids from the food, is lost in the stools as calcium soap, whereas the companion ion, chlorid, is nearly entirely absorbed and must be covered in the body fluids by base other than the ingested base. The quantity of chloridion absorbed being unusually large, a higher level of conveyance is necessary and base for this is obtained at the expense of bicarbonate.

Diagram 4 shows the measurements describing a moderate chlorid acidosis in the plasma of a child afflicted with tubular nephritis. Here, the bicarbonate change is seen to be due to an appreciable reduction of base and a large increase of chlorid, the effect of change in these two factors on bicarbonate being considerably offset by a decrease of R′, which may be explained as the result of the low plasma protein found in this disease. These findings are fairly characteristic of tubular nephritis. In the so-called glomerular form of nephritis various distortions of plasma structure may occur.

Diagram 5 will serve to illustrate one type of change. Here, total base and chlorid values are approximately normal and bicarbonate reduction is referable to an increase of R′, apparently due to retention of some factor or factors contained in this value.

Diagram 6 shows the commonest cause of acidosis. This cause is ketosis; that is, the accumulation in the body fluids of incompletely oxidized fatty acids in the form of beta-oxybutyric acid and diacetic acid. These acids must be covered by fixed base while being conveyed for excretion in the urine. The area designated K′ in the diagram shows how extensively they replaced bicarbonate ion in the blood-plasma of a child entering the hospital in diabetic coma. According to the diagram there has been no depletion of plasma base by the unusually large amount of acid claiming excretion in the urine. That is, the regulatory factors in control of the process of acid excretion are evidently operating accurately. The bicarbonate reduction is thus entirely referable to the concentration of ketone acids. This diagram is also descriptive of bicarbonate reduction by the ketosis accompanying various other abnormal conditions; such, for example, as starvation, cyclic vomiting and infectious diseases.

Diagram 7 describes an interesting situation which will serve to fur-

ther illustrate the interdependence of the acid-base factors in the plasma. They are from a child with an upper intestinal obstruction. The diagram shows an increase of bicarbonate, a large concentration of ketone acids and an extensive loss of chlorid. Alkalosis in the presence of ketosis is an unusual event. It is here readily understandable, however, as the result of a recession of chlorid which is of greater extent than the accumulation of ketone acids. The chlorid loss was due to vomiting of stomach secretions and the ketosis, presumably, to starvation. It is of interest to note how greatly the presence of ketone acids has limited bicarbonate increase, preventing an alkalosis of possibly fatal degree. These data will also serve to remind us that ketosis and acidosis are not synonymous terms, and that the finding of acetone bodies in the urine does not constitute necessarily a diagnosis of acidosis.

TREATMENT

Since change in the plasma bicarbonate is to be regarded as a secondary event and in the nature of an adjustment, it is obvious that in the presence of acidosis or alkalosis correct choice of therapeutic measures depends on recognition of the underlying disease and knowledge of the alterations in the acid-base structure of the plasma which it may cause. The several types of abnormal circumstances which may bring about distortion of plasma structure can be briefly indicated: (1) Conditions which interfere with the reabsorption of digestive secretions and thereby cause depletion of plasma materials; (2) impairment of renal function with consequent inaccuracy of control of the concentrations of plasma substances; (3) depression of the level of carbohydrate metabolism permitting accumulation of incompletely oxidized fatty acids. The plasma changes which are fairly characteristic for each of these three groups of disease conditions are illustrated by actual examples by the diagrams in Figure 2. This information permits selection of the correct agent for plasma repair from the several simple materials at hand, namely, sodium chlorid, sodium bicarbonate and glucose. It should be mentioned here that, although repair of the plasma by such agents is often most urgently indicated, we should regard our attempts in this direction only as a means of gaining time in which to combat the underlying disease.

Correction of an abnormality of body fluid reaction caused by depletion of plasma materials in conditions producing a continued loss of digestive secretions is usually incidentally attained by repair of the more serious accompanying body fluid change, namely, reduction of the volume of the blood-plasma and of the interstitial fluids. The treatment of dehydration consists essentially in administration of physiological salt solution by subcutaneous injection. The one important requirement in this extremely simple therapeutic undertaking is that an adequate amount

of salt solution be supplied. The alkalosis or acidosis being due to loss of sodium and of chloridion from the plasma in differing relative amounts, restoration of body fluid volume by means of sodium chlorid solution also provides the materials necessary for reëstablishment of the bicarbonate concentration; the kidney, after volume is regained, being capable of regulating the excretion of sodium and of chlorid, individually, in terms of their normal plasma values. In the case of alkalosis, dilution of the blood-plasma with salt solution tends at once to reduce bicarbonate. When acidosis is present, this dilution effect may cause further reduction of bicarbonate during the often considerable interval before volume restoration is complete. There is, thus, theoretical indication that, in the treatment of dehydration accompanied by severe acidosis, an initial injection of sodium bicarbonate solution will serve the purpose of controlling acidosis during the interval required for repair of dehydration by the administration of physiological salt solution. Experience has shown that this is a useful procedure in the case of dehydrated infants exhibiting severe acidosis, but otherwise is an unnecessary measure. It has also been found that, preceding reëstablishment of renal function, the administration of physiological sodium chlorid solution sometimes causes the concentrations of fixed base and of chloridion to rise above their normal levels. Avoidance of this probably seriously incorrect situation can usually be obtained by supplying 10 per cent glucose solution intravenously; the effect of this measure being to lower the concentrations of fixed base and of chloridion by dilution and also to promote kidney activity upon which a correct control of these concentrations depends. Another helpful effect produced by the glucose solution is that it often greatly accelerates the absorption of salt solution delivered subcutaneously, presumably by causing a transient hypertonicity of the blood-plasma. These considerations render the intravenous administration of glucose solution so important an accessory measure that, when practicable, it should be routinely used in the treatment of severe dehydration. It should be remembered that glucose solution cannot directly repair a reduction of body fluid volume, since this requires not only replacement of water, but of the structural factors, sodium and chlorid, as well. It may be mentioned here that the introduction of physiological salt solution by intraperitoneal injection is a justifiable, indeed often a life-saving, procedure especially in the case of infants severely dehydrated by diarrheal disease.

The acidosis occasionally present in nephritis can be directly treated only by the intravenous injection of sodium bicarbonate solution, a procedure which presumably ill suits the underlying situation. Fortunately, except in the nearly terminal phase of the disease, a severe degree of acidosis is rarely encountered, and direct treatment is not required. Indeed, it is quite possible that, in tubular nephritis at least, the increased plasma acidity should be regarded as a helpful adjustment. The distressing

hyperpnea which sometimes develops in the final stage of nephritis can be removed, and probable death from acidosis prevented, by the intravenous injection of sodium bicarbonate solution, with the result that the more usual terminal events are permitted to take their course.

The logical agent for the treatment of acidosis due to ketosis is obviously glucose, since, if the level of carbohydrate metabolism can be raised sufficiently, the concentration of ketone acids in the plasma will be removed and the base which they covered will again compose bicarbonate. If the situation is urgent, glucose must be given intravenously, and if the ketosis is due to a diabetic inability to oxidize glucose, insulin must of course also be supplied. According to Diagram 6, there has been no loss of fixed base from the plasma and bicarbonate reduction is entirely referable to the space occupied by the ketone-acid concentration. Removal of these acids should completely restore bicarbonate. There is, therefore, no indication for an attempt to directly repair the bicarbonate concentration by administration of sodium bicarbonate. When the relationship of increased plasma acidity to bicarbonate reduction was defined some fifteen years ago, it was an easy and apparently correct inference that the indicated procedure was to vigorously supply the lacking substance. The bicarbonate therapy of acidosis was begun with enthusiasm. It has since been the evidence of clinical experience as well as of theoretical considerations that the treatment of acidosis due to ketosis by administration of sodium bicarbonate is not only unnecessary but may be actually harmful. This statement must be somewhat qualified in the case of diabetic ketosis. Apparently the action of insulin is more rapidly effective if an extremely abnormal acidity of the plasma be somewhat reduced by an initial injection of sodium bicarbonate solution.[5] This procedure is unnecessary in the great majority of cases of diabetic ketosis and, out of respect to the theoretical and empirical objections to the use of sodium bicarbonate, should be applied only in the presence of a dangerously severe acidosis. It is a point of importance that most clinical situations presenting acidosis due to ketosis have also produced a considerable, often an extensive, degree of dehydration. There is, therefore, usually an indication for the giving of salt solution to repair dehydration in addition to administration of glucose for removal of ketosis.

An interesting situation from the therapeutic point of view is described by Diagram 7 in Figure 2. Here the requirements are that a greatly lowered chloridion concentration be restored and a large accumulation of ketone acids be removed. Evidently if chlorid be raised faster than ketone acids are removed, too extensive bicarbonate reduction and acidosis may be produced. On the other hand, if ketone acids be too rapidly removed, further increase of bicarbonate may result. Unfortunately for

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[5] This statement is based on excellent data recently shown us by A. V. Bock of the Massachusetts General Hospital and is cited with his permission.

a theoretical accuracy of procedure, it is not practicable to gauge the use of salt solution and of glucose according to these considerations. The clinical circumstances of such a situation demand that both these agents be employed as energetically as possible. The ketone acids may be expected to disappear more rapidly than chloridion can be replaced, with the result that to some extent alkalosis will be increased; an event, however, of slight significance as compared with the benefit gained by repair of dehydration.

Having considered the rationale of the use of the several essential reparative agents according to clinical circumstances, a few points of detail regarding methods and extent of administration may be briefly presented. Since correction of bicarbonate change by administration of physiological salt solution depends on appropriate adjustment by the kidney of the excretion of sodium and of chloridion, this result cannot be expected until body fluid volume has been completely restored. The all important requirement is, therefore, that the quantity of salt solution supplied be sufficient to remove the underlying dehydration. If dehydration is of an evidently dangerous degree and attempts at repair by the sub-cutaneous route seem inadequate, the more rapid methods of supplying salt solution by intraperitoneal or by intravenous injection are indicated. If an intravenous injection of 10 per cent glucose solution be used, it should be given directly following the subcutaneous administration of salt solution. The minimal quantity of glucose solution or of physiological salt solution required by intravenous injection is usually from 20 to 30 c.c. per kilogram of body weight. The intravenous injection of solutions is often difficult in the case of severely dehydrated infants and the attempt may often be wisely omitted in favor of the intraperitoneal method of supplying salt solution. The clinical evidences of satisfactory repair of dehydration are return of the natural turgor and elasticity of the skin, disappearance of dryness of the tongue and mucous membranes, and secretion of a normal volume of urine. When acidosis is present, the effect of therapy is often strikingly indicated by the disappearance of hyper-pnea.[6] It should not be forgotten that, until the circumstances causing

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[6] Helpful data, which can be obtained by relatively simple and dependable methods of analysis from a small sample of blood-plasma or serum if laboratory facilities are at hand, are measurements of the concentrations of bicarbonate, chlorid and protein. The bicarbonate value is the most useful of these since it directly defines the degree of acidosis or of alkalosis and measures the effect of treatment. The chlorid measurement will usually explain an increase of bicarbonate and describe the extent of repair obtained by administration of sodium chlorid solution. It should be remembered that the concentration of chlorid in the plasma is not an index of the degree of dehydration since various circumstances may cause extensive body fluid loss without altering the plasma chlorid value appreciably. The concentration of the plasma proteins as deter-mined by the refractometric method provides a fairly satisfactory indication of the degree of dehydration of the plasma. This datum can be easily and quickly obtained provided the expensive instrument which it requires is at hand.

dehydration have been removed, the measures in support of body fluid volume will have to be energetically continued. It may be necessary to repeat the injections of the indicated solutions at intervals of eight to twelve hours. Although in urgent situations the parenteral method of supplying the reparative agents is imperative, it is often possible to provide water and materials to a considerable extent by way of the gastro-intestinal tract; by nasal or rectal drip or even by mouth, if vomiting does not completely prevent. An effective and pleasant tasting mixture may be prepared from the following materials: One part each of physiological sodium chlorid solution, orange juice, and water; three parts of 10 per cent glucose solution and sodium citrate to provide a concentration of 1 per cent. With improvement in the condition of the patient these measures replace the parenteral administration of materials, and in conditions producing dehydration of moderate severity they may alone suffice.

In the infrequent situations, mentioned above, in which direct repair of a lowered plasma bicarbonate seems indicated, a 4 per cent solution of sodium bicarbonate may be given intravenously to the extent of 20 to 30 c.c. per kilogram of body weight. The treatment of acidosis in the great majority of instances consists in the removal of ketosis and the clearly indicated therapeutic agent is glucose. Although the emphasis is here on glucose, it should not be forgotten that the abnormal circumstances which tend to produce dehydration usually accompany ketosis as clinically encountered. Often the accompanying dehydration is so severe as to require energetic and extensive treatment. When the ketosis and dehydration are not of a severity which requires parenteral treatment, the measures mentioned above for the introduction of reparative materials by way of the gastro-intestinal tract may be used.

The successful treatment of a severe acidosis or alkalosis often depends on an almost immediate institution of correctly chosen measures. Usually the time required for definition of the situation by laboratory methods is not available. The efficacy of therapeutic attempt, therefore, will be largely determined by the accuracy of an appraisement of clinical circumstances and evidences in terms of probable pathogenesis.

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CHAPTER XXX

TREATMENT OF ASPHYXIA DUE TO DROWNING, ELECTRIC SHOCK, AND CARBON MONOXID

William R. Redden

Asphyxia is the immediate result of an anoxemia or oxygen deprivation in living animal cells. It may be partial or complete, *i.e.*, it may involve one group of cells, one or more organs, or the organism as a whole. Death of one part of the organism or of the whole, and the reversibility of the anoxemic process depend upon the length of time tissues vital to life are exposed to oxygen lack, and upon the limit of their selective tolerance to this condition.

Numerous investigations since 1667 have demonstrated in experimental animals the difference in tolerance to total oxygen deprivation of the various groups of nerve cells which form the central nervous system. Hayem and Barrier analyzed results up to 1887, and Hill up to 1900. Reference to this work is also made by Batelli, Prus, and D'Hallium, but the most extensive investigations since 1905 have been conducted by Stewart, Guthrie, Burns, Pike, Crile, Dolley, Cannon and Burket. Table I indicates the difference in viability of these parts following sudden and complete oxygen deprivation, as reported by Cannon and Burket.

TABLE I—Periods of Resistance of Nerve Cells to Oxygen Deprivation

Cerebrum, small pyramidal cells	8 minutes
Cerebellum, Purkinje's cells	13 minutes
Medullary centers	20-30 minutes
Spinal cord	45-60 minutes
Sympathetic ganglions	1 hour
Myenteric plexus	3 hours

It will be seen that the higher centers are particularly susceptible to oxygen lack and that the medulla, which includes the respiratory center, tolerates anoxemia about three times as well as the cerebrum and about twice as well as the Purkinje's cells. But the important fact is that the respiratory center has a tolerance to oxygen deprivation ranging from twenty to thirty minutes, for once this center reaches an irreversible anoxemia, death is inevitable. Pike *et al.* believed that the time limit of total anemia of the central nervous system after which complete resuscitation is possible is probably below twenty minutes; this is about the

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same as set by Batelli. Crile and Dolley in experiments on dogs indicate a limit of between six and seven minutes with an ulterior limit under ten minutes; Mayer sets ten to fifteen minutes; Hayem says brain functions are not recovered after from ten to eleven minutes.

On the other hand, it is well known that the heart is one of the most hardy of the organs essential to life, for it has been known to beat hours after clinical death, even when there is no evidence of either a heart or a pulse beat. Parrium found rhythmical right auricular beats in a rabbit's heart fifteen hours after death; Vulpian noted heart beats in a dog ninety-three hours and thirty minutes after death; Regnard and Loye observed heart beats lasting about an hour after the execution of a criminal, and Rousseau found heart beats of a human at autopsy twenty-four hours after death. For this reason these ordinary signs of death must be discounted and rigor mortis must remain the real test of death. For even though the heart beat ever so feebly it may be able to furnish a sufficient amount of oxygen to vital tissues to prevent death, particularly when the bodily activities are reduced to a minimum and the important factor of oxygen conservation exerts its influence.

Although experimental evidence indicates the relative tolerance of tissues to sudden oxygen deprivation, the actual figures given cannot be applied to asphyxiation as it usually occurs in man because of the impossibility of measuring the many variables involved. But this does not change the order in which the cells of the central nervous system succumb to anoxemia. With these facts in mind it is not difficult to understand most of the phenomena involved in the asphyxia of drowning, electric shock and carbon monoxid, a group which stands apart from other forms of asphyxia because it is composed of the three outstanding causes' of this type of accidental death, and because this group as such has been carefully studied by numerous scientific commissions since 1911 in an attempt to evaluate and standardize methods of resuscitation.

Drowning.—Drowning leads the group in the number of fatalities in the United States for it causes approximately 7,000 deaths annually. The general trend of fatalities in this country is indicated in Table II, taken from the United States Census Bureau reports of 1921 to 1924 inclusive.

This table indicates that drowning as a cause of death has shown a slight tendency to decline as the population has increased. This may be due to the vast amount of educational work which has been carried on to an increasing degree in the field of water safety, rescue and resuscitation. There is evidence of a further decrease during the next three years. Although accurate figures are not available it is generally agreed by organizations particularly well informed on the subject that between 5,000 and 6,000 apparently drowned people are resuscitated each year in the United States.

Drowning represents the simplest type of asphyxiation of this group,

Year	Total	Rate per 100,000
1921	7044	8.1
1922	6678	7.1
1923	6677	6.9
1924	7154	7.2

for as the victim becomes completely submerged, the respiratory tract is immediately cut off from a supply of air. However, this does not mean that the respiratory center and the heart are immediately robbed of a sufficient supply of oxygen to cause a fatal anoxemia such as is produced in experimental animals, for there is without question a conservation of oxygen in the alveolar spaces, in the blood, and in the tissues, which may delay complete anoxemia in the submerged victim, and which no doubt accounts for the reports of successful resuscitation of victims who have been submerged for a time much longer than that named in Table I. Experience, however, indicates that submersion may produce an irreversible condition within five minutes, or that such a condition may be delayed for thirty minutes, the average ranging from ten to twenty minutes.

Water in the Respiratory Passages.—There has been considerable discussion about the presence of water in the upper air passages and in the lungs of victims of submersion. De Haen, in 1772, showed that water entered the lungs of submerged dogs; and the First Resuscitation Commission of the Royal Medical and Chirurgical Society reported in 1862 that water was drawn freely into the lungs during the act of drowning; Schaefer's experiments on dogs indicate a wide variation in the amount of water exchanged during immersion without any special regard to the size of the animal; but Paltauf demonstrated that, although water entered the respiratory passages, it was rapidly absorbed. Schaefer confirmed this in his experiments and found that as much as 740 c.c. of water were taken in and that much of it was absorbed. The following represents the opinion of physiologists to-day. Water may enter the upper respiratory tract and even beyond, but any amount which may reach beyond is so rapidly absorbed that it does not constitute a practical problem in the resuscitation of a victim of submersion, whether or not he requires artificial respiration. Cannon states that water may be prevented from entering the respiratory passages, in cases of submersion, by a sudden spasm of the respiratory muscles due to the shock sustained as water reaches the trachea. Of course, victims submerged in water for a time beyond that from which they can be resuscitated may show considerable water in the bronchioles,

atria and even in the alveoli, but the reason for this is obvious. On the other hand, there is evidence that indicates that if water reaches the alveolar spaces and is not absorbed, none of the methods formerly in use, such as barrel rolling, inversion and sudden abdominal compression, can possibly remove this water. This is indicated by attempts to force fluid from the respiratory tract of two influenzal pneumonia patients at the Naval Hospital, Chelsea, Massachusetts, in 1918. Each patient, unconscious and about to die of respiratory failure, was inverted by one operator so that the chest came against his knees, then the second operator applied as much pressure as possible to the lower ribs as in the prone pressure method of artificial respiration. Only about a third of a glass of serosanguinous fluid could be obtained from each, yet at necropsy performed within a short time, over a pint and a half of this fluid was readily expressed from the lungs of each by moderate direct compression. For these reasons an attempt to remove water from the lungs is a waste of precious time. Furthermore, such efforts may cause serious damage because they bring direct pressure upon such greatly congested organs as the liver, stomach and intestines. Moreover, the prone pressure method of artificial respiration properly carried out gives ample drainage for both the respiratory passages and the stomach, and the first application of dorsal pressure is usually sufficient to clear the air passages of any serious amount of water or other materials.

Symptoms.—Victims of submersion are usually chilled and cyanotic, breathing may or may not have ceased, the pulse and heart beat may or may not have stopped. They frequently appear dead, and are often declared so by physicians and yet such victims have often been resuscitated.

Electric Shock.—Electric shock causes fewer deaths in the United States than either drowning or carbon monoxid. It is probable that at least 1000 cases of electrocution are resuscitated annually in the United States and Canada, although there are no reliable figures to prove this.

Table III presents the electrical fatalities from 1911 through 1924, in the United States, Canada, England, Wales, and Switzerland. This is part of a report by the Engineering Committee of the Conference on Electric Shock of which Philipp Drinker is chairman.

It will be seen that in spite of the rapid expansion of the electrical industry in this country the number of fatalities due to electric shock has remained remarkably low even though it has kept pace with the increase in population, with a tendency toward a rise. It is also noticeable that the death rate in England and Wales has likewise remained low, and in general lower than in the United States, and that the death rate in Switzerland is less than in the other countries.

Asphyxia from electric shock is produced in one of three ways: (1) By primary cardiac failure; (2) by primary respiratory failure; (3) by a combination of the two. In general the type of failure depends on the

TABLE III—ELECTRIC FATALITIES (EXCEPTING LIGHTNING) FROM 1911 TO 1924

Year	United States and Canada, Metropolitan Life Insurance, Industrial Dept.		United States		England and Wales		Switzerland	
	Number of Deaths	Deaths per 100,000	Number of Deaths	Deaths per 100,000	Number of Deaths	Deaths per 100,000	Number of Deaths	Deaths per 100,000
1924...	134	0.9	975	1.0	38	0.09	26	0.7
1923...	106	0.7	945	1.0	25	0.06	23	0.6
1922...	107	0.8	842	0.9	22	0.04	29	0.7
1921...	112	0.8	741	0.8	19	0.05	25	0.6
1920...	117	0.9	822	0.9	26	0.07	42	1.1
1919...	115	0.9	748	0.9	32	0.08	29	0.8
1918...	115	1.0	754	0.9	40	0.11	38	1.0
1917...	78	0.7	654	0.9	24	0.06	25	0.7
1916...	100	1.0	586	0.8	34	0.09	25	0.7
1915...	66	0.7	515	0.8	29	0.08	19	0.5
1914...	69	0.7	553	0.8	20	0.05	18	0.5
1913...	85	1.0	670	1.0	22	0.06	20	0.5
1912...	72	0.9	567	0.9	23	0.06	25	0.7
1911...	60	0.8	513	0.9	..	...	25	0.7

voltage of the current and the length of time it passes through such vital organs as the brain or heart, or both. It is evident that there are too many variables involved in accidental electrocution in man to determine the amount of current which has passed or is passing through the heart or nervous system of a victim, except in rare cases in which a known current pressure passes through perfectly applied electrodes similar to the conditions which obtain in the electrocution of criminals. Prévost and Batelli appear to be the first investigators to perform extensive experiments on electric shock in animals under conditions sufficiently controlled to warrant their conclusions. Their work, as well as that of other investigators, was carefully reviewed and analyzed by Jex-Blake in 1913, in four Gaulstonian lectures. He accepted the conclusions of Prévost and Batelli and, by comparison with observations made on the effects of varying electric currents on man, applied their deductions to human victims. Urquhart, in 1927, confirmed the deductions of former observers as to the cause of death by electric shock in experimental animals. *Primary cardiac failure* is usually due to the passage of low voltage currents (70 to 500 volts) through the heart in which it produces an irreversible ventricular fibrillation. The victim is conscious and breathing, his face is white, not cyanotic, the pulse and heart beat are absent. After from one to five minutes during which he may even talk, he suddenly collapses, becomes unconscious, stops breathing, and dies irrespective of treatment. Death is due to an anoxemia of the heart and respiratory center. Onlookers usually consider

such victims good subjects for artificial respiration. Occasionally this ventricular fibrillation stops spontaneously, and the normal heart beat may return. Robinson and Bredeck report the case of a woman who had three attacks of syncope each lasting about four minutes; during one attack the patient ceased breathing and showed no signs of a heart beat; an electrocardiogram characteristic of ventricular fibrillation was obtained; the patient recovered and lived for thirty hours. Dieuaide and Davidson also report a case of recovery. Boorutan, in 1918, from a study of fatal accidents in Germany, reported that 90 per cent of fatalities from electric shock were due to ventricular fibrillation. Ram, in an analysis of electric accidents in England from 1912 through 1921, states that when artificial respiration was applied to victims who had received under 250 volts, only 39 per cent were saved as against 62.5 per cent in those who had received over 650 volts. Urquhart indicates that Ontario reports on electric shock victims confirm these observations.

Primary respiratory failure is usually caused by the passage of high voltage electric currents (500 volts and over) through the nerve centers of the brain with a consequent block of nervous impulses, particularly those from the respiratory center. The victim is unconscious from the beginning, cyanotic, and is not breathing, but the pulse and heart beat persist for a short time. Such cases offer the best chance for recovery, provided artificial respiration is applied immediately and is continued long enough. Probably 75 to 80 per cent of such cases recover under this treatment, but time lost in its application usually means a fatal outcome.

Combined cardiac and respiratory failure may be caused by the passage of either high or low voltage currents through the nerve centers, particularly the respiratory center, and the heart. The nerve center impulses become blocked and the heart goes into ventricular fibrillation. The victim appears dead, for he is unconscious, cyanotic, pulseless and not breathing. But in spite of the seriousness of the condition it may be reversed by artificial respiration if promptly and properly applied.

TREATMENT FOR DROWNING AND ELECTRIC SHOCK

Artificial respiration offers the only hope for recovery in cases of drowning and of electric shock, irrespective of the condition produced. If there is any chance of reversing ventricular fibrillation by any procedure, it rests in a possible gentle massage of the heart as artificial respiration is given. Artificial respiration by the prone pressure method properly applied over a sufficient period will do more than any known drug to revive any type of case. But it must be applied immediately and continued until normal respiration is reestablished or until marked cooling of the body or rigor mortis indicates death. All other signs should be totally disregarded for they have been present in hundreds of victims who have been

resuscitated even after physicians have pronounced them dead. Of those victims who recover, the majority begin to breathe within from five to thirty minutes, some require treatment for an hour or more, and one case cited by Maclaclen was treated for eight hours before normal respirations started.

A report by the Engineering Committee of the Conference on Electric Shock with Philipp Drinker as chairman gives the best evidence of the value of the prone pressure method of artificial respiration in electric shock, for the report includes only carefully recorded cases which come up for the Insull and Canadian bronze medals. The report which covers the period from 1918 to 1928, shows a total of 265 cases treated by the prone pressure method; of this group 200 or 76 per cent recovered and sixty-five or 24 per cent died, no other cause of death being apparent than failure to restore respiration. It further shows that among 202 cases in which resuscitation was applied within three minutes after the shock, 158 or 78 per cent were successful; and among sixty-three cases in which over three minutes had elapsed forty-two or 67 per cent were successful. An analysis of the length of time it took to resuscitate victims who had received voltages varying from 749 and under to 40,000 and over would seem to point to an average of from fifteen to twenty minutes. But a certain number of cases required from thirty minutes to eight hours before normal breathing was reëstablished. In three cases the bodies were reported as "rigid." In practically all cases, the resuscitator reported that the victims were "unconscious and not breathing." The time reported was estimated rather than measured, but nevertheless throws some light on the problem.

The usual treatment for shock should always be instituted in these cases; that is, the application of heat, friction of the extremities without exposure, declination of the body toward the head. When the victim becomes conscious stimulants such as aromatic spirits of ammonia, hot drinks such as coffee or tea, may be given by mouth. Caffein sodium benzoate 0.5 grams (7½ grains) may be of value if given intravenously at any time the pulse beat can be felt. It is common practice, especially among laymen, to give aromatic spirits of ammonia inhalations to unconscious people but this drug is known to reduce blood-pressure and is, therefore, contra-indicated until the circulation has been established. Lobelia has been commonly used as a respiratory stimulant, but recent studies by Norris and Weiss show that it may cause serious results and should not be used. Adrenalin chlorid might raise the blood-pressure in the coronaries if given in such a way as to reach the heart, but it may cause disastrous results in cases of cardiac depression due to asphyxia. The victim should be kept absolutely quiet in a reclining position for a number of hours after recovery and should on no account be left alone during this time, particularly in electric shock, for victims of electric shock frequently stop breathing after periods of normal respiration. Many victims of

electric shock have been resuscitated by linemen and other first aiders only to die on the way to a hospital of suffocation because breathing stopped and the ambulance attendant did not know how to give artificial respiration. Counter shock methods such as pounding the soles of the feet or dilatation of the anal sphincter or general rough handling are simply relics of the days of prejudice and superstition and have no place in medical practice or first aid work.

W. H. Howell is chairman of a committee organized by Simon Flexner at the instigation of Lieb of the New York Edison Company in 1926, to conduct systematic research in electric shock, electric accidents, and resuscitative and preventive measures. From investigations of this and similar committees will no doubt come important advances in our knowledge of electric shock. Already Hooker and Wiggers, in a study of experimental ventricular fibrillation produced by an electric current in animals, have been able to stop the fibrillation and then to restore normal heart beats. Animals were kept alive for at least twenty-four hours. This may point the way to a sure method for stopping ventricular fibrillation resulting from electric shock.

CARBON MONOXID ASPHYXIA

Carbon monoxid, a colorless, odorless gas, slightly lighter than air, constitutes the chief hazard in asphyxiation from gases, smoke and fumes, and because of its combination with other irritating substances it becomes even more hazardous than when inhaled in pure form. It is found in lethal quantities in illuminating gas, coal gas, from stoves and heaters closed too soon after refueling, natural gas used in imperfect appliances as shown by Jones, Berger, Holbrook, Brumbaugh, Hayhurst and Monger. It is also present in gases around blast furnaces, and in mines, in smoke from burning buildings, in exhaust gases of automobiles as shown by Fieldner, Straub, Jones, Henderson, Haggard, Teague, Prince and Dunderlich, and in gases given off by charcoal heaters. It is evident that the danger of asphyxiation from carbon monoxid gas is almost universally present. Investigations by Henderson and others indicate that the average automobile discharges about 2 cubic feet of this gas per minute, and that small cars like the Ford eject at least 1 cubic foot of this gas per car, per minute, enough to render a closed garage deadly in five minutes. Reports from the United States Census Bureau on fatalities from gas, from 1921 through 1924 (the latest available), appear in Table IV.

It is evident from this table that during these four years there was a gradual increase in the total number of deaths and, what is more significant, in the death rate per hundred thousand. This means that fatalities from gas poisoning have not only kept pace with the increase of population but have gradually gained. Drinker states that in 1926 the emergency

TABLE IV—FATALITIES FROM CARBON MONOXID POISONING
IN THE UNITED STATES FROM 1921 TO 1924

Year	Total	Rate per 100,000
1921	3179	3.6
1922	3487	3.7
1923	3913	4.0
1924	4166	4.2

crews of the Consolidated Gas Company of New York responded to 1,222 calls. Of this number 467 persons died and 755 recovered; using this relation as an approximation against the total number of cases in 1924, there were 6,750 cured cases in 1924 and a total of 10,916 possibly seen by physicians. Although such estimates are open to criticism, they nevertheless help to indicate the importance of the problem.

The Action of Carbon Monoxid.—It is well understood by physiologists that the effect of carbon monoxid both in animals and in man results from an anoxemia of vital organs rather than from any direct deleterious effect on the cells themselves. This anoxemia, relative or total, is due to the fact that carbon monoxid, by its ability to combine with the hemoglobin molecule 300 times more readily than oxygen, rapidly displaces the oxygen of the blood and tissues. However, this process is reversible provided a sufficient amount of oxygen to overbalance this 300 to 1 ratio can be introduced into the alveolar spaces and thence into the blood stream before organs essential to life have succumbed to oxygen deprivation.

The symptoms of carbon monoxid asphyxia depend on the concentration of carbon monoxid in the inhaled air and on the length of time the victim is exposed to this concentration. Mild cases of asphyxia from this gas usually complain of malaise, headache, dizziness or nausea. More severe acute cases present the same symptoms but more marked, and in addition complain of weakness. In fact, all these symptoms may be blurred as weakness strikes in, affects the knees, causes collapse and prevents the escape of the victim; then follows unconsciousness and death due to respiratory failure. The whole process may not require more than five to ten minutes but may take from fifteen to thirty minutes.

A majority of gas victims are found after hours of exposure to the gas in various concentrations, usually low. For this reason they are either dead when found, or are unconscious, breathing more deeply and more rapidly than normal, and have a high pulse rate, or are beginning to show shallow, rapid, irregular breathing indicative of a beginning respiratory failure, and a rapid shallow pulse. Analysis of this majority group by Cannon and Drinker indicates that once breathing has ceased, there is little hope of recovery irrespective of treatment. However, these cases

should not be confused with those which have just stopped breathing after a relatively brief exposure to high concentrations of the gas.

Victims of this relatively slow asphyxia may remain unconscious for days or even a week or more and then die of respiratory failure, or they may slowly recover with or without unpleasant sequelæ. Cannon and Drinker, in an investigation of 860 hospital cases, discovered that 59.8 per cent were unconscious when admitted, or were reported unconscious when found, and 44 per cent were breathing rapidly. Only in rare cases was breathing very slow. The average pulse rate was 104. Of these, 6.4 per cent were frothing at the mouth, 17.4 per cent showed râles in the lungs, 4.5 per cent had pulmonary edema. They conclude from these data that resuscitation measures in gas poisoning cases must, in large measure, be applied to unconscious victims who have rapid heart beats, and who in a large percentage of cases have excess fluid in the respiratory tract. Pneumonia occurred in 9.4 per cent, and the death rate for the group was 14.5 per cent. They point out that all these cases had passed beyond the stage of first aid treatment and had become hospital cases. The reports of Thompson, in 1904, in a clinical study of ninety cases of poisoning from illuminating gas, and Lämpe, in 1921, show some variation from these findings but in general they are similar. Most of the moderately severe and severe cases which recover complain of a severe headache which may last for days. This headache gives the feeling that the brain is in a vice-like grip. Forbes *et al.* present evidence that this is caused by an edema of the brain which actually increases intracranial pressure.

Treatment of Carbon Monoxid Asphyxia.—It is evident from the foregoing that the treatment of such cases must be directed not only toward the restoration of respiration in those who have ceased to breathe but, what is equally important, it must include the rapid detachment of carbon monoxid from the hemoglobin molecule, in order to prevent further asphyxiation. This is accomplished by artificial respiration plus the use of a special inhalator, or the inhalator alone if the patient is breathing.

Since the report of Haggard and Henderson in 1922, on the beneficial effect of a mixture of carbon dioxid 5 per cent and oxygen 95 per cent, in such cases, by use of the H-H Inhalator, a vast amount of evidence has been forthcoming from gas companies, hospitals, fire and police departments, etc., both in the United States and abroad, which indicate that the inhalation of such a mixture removes carbon monoxid more rapidly than any other method, that it clears up unpleasant symptoms within a few minutes, in cases mildly gassed, and that when used in acute cases of partial or total asphyxiation, it not only offers the best chance for rapid recovery but it also frequently eliminates such postasphyxiated symptoms as the characteristic "splitting headache," nausea and vomiting, and helps to lessen the possibility of unpleasant sequelæ such as paralysis and pneumonia.

The use of such a mixture is based on sound physiological grounds. For, as indicated above, the speed of reversibility of carbon monoxid anoxemia depends upon the rapidity with which this gas can be replaced by oxygen. The replacement of CO by oxygen in the hemoglobin molecule depends on the amount of oxygen that is made available to red blood-cells as they pass through the alveoli of the lungs. This in turn depends on two factors, the amount of lung ventilation and the quantity of oxygen inhaled. It is well known that carbon dioxid is the normal stimulant of the respiratory center and that if given in proper amounts both to normal individuals or to victims of partial asphyxia, it will increase the respiratory volume from three to four times. Thus when carbon dioxid and oxygen are properly combined and given to victims of asphyxiation from CO gas, there is brought about the most favorable opportunity for the displacement of CO by oxygen in the hemoglobin molecule and the consequent rapid relief of vital organs from anoxemia. Although the H-H Inhalator was adopted unanimously by the Resuscitation Commission in 1922, there has since developed some discussion as to the value of carbon dioxid in cases of gas asphyxiation. Sayers and Yant, Rossiter, and others have reported that the CO_2 does not necessarily increase respiratory exchange and that oxygen alone eliminates CO about as rapidly as the mixture of CO_2 and O. If this is true it is of great importance because it is a simple matter to obtain an ample supply of oxygen, whereas it is not simple to obtain CO_2. However, Binger, Faulkner and Moore have demonstrated in dogs, rabbits, guinea-pigs and mice that oxygen in concentrations of over 70 per cent of an atmosphere is poisonous, that the poisonous effects manifest themselves in drowsiness, anorexia, loss of weight, increasing dyspnea, cyanosis, all of which are the result of oxygen want; that the cause of oxygen want is a destructive lesion of the lungs which may be characterized grossly as a hemorrhagic edema which affects the diffusion membrane. Moreover, oxygen under certain conditions is a respiratory depressant as seen in the production of apnea. Even with the use of the CO_2 and O mixture it has been found advisable to stop treatment as soon as possible because of the oxygen content and in no instance to use it for over forty minutes without interruption. But there is one factor in the evidence of these opponents to the addition of CO_2 which has not been given sufficient consideration; namely, that in cases of CO asphyxia there is developed a high degree of alkalosis in the blood which may cause such a rapid utilization of CO_2 for a time that the presence of 5 per cent has no stimulating effect on the respiratory center until a proper acid alkali balance has been restored. This would lead to the conclusion suggested by Drinker, that it would be advisable to temporarily increase the CO_2 content of the mixture rather than to eliminate it.

In 1925 Haldane stated "not only does carbon dioxid, by increasing greatly the depth of breathing, hasten, in corresponding degree the elim-

ination of carbon monoxid from the blood, but the carbon dioxid itself gives marked immediate relief to the anoxemia. It does so by enabling the circulation, kept in check by the alkalosis produced by increased breathing of CO poisoning, to increase at once, thus carrying much more oxygen to the tissues. The mixture of carbon dioxid and air is, I think, superior to pure oxygen, though inferior to the mixture of oxygen and carbon dioxid." (See description of inhalator.)

In addition to the use of artificial respiration and the inhalator in cases of gas poisoning, the other measures already mentioned under treatment for electric shock and drowning should be used. It should be constantly borne in mind that these cases of asphyxia are in extreme shock and should, therefore, be treated for this condition. Probably heat and the declination of the body toward the head, along with absolute rest in a reclining position for at least three or four hours after recovery will accomplish more than any drug.

ARTIFICIAL RESPIRATION

Probably attempts to resuscitate the dead or apparently dead have been made since man first saw his fellow man die, and it is possible that the miraculous restoration of life occasionally recorded in the Old Testament represents successful results. But no organized effort to assemble accurate data and to standardize methods was made until the organization of the Amsterdam Society in 1766 and of the Humane Society of London in 1774. Both societies were chiefly concerned with the resuscitation of victims of submersion, and gave their attention to the evaluation of methods already in common use chiefly among laymen, rather than to the development of new methods. As the result of the investigations of the London Society, mouth to mouth and the simple fireplace bellows methods of insufflation gradually gave place to the application of heat, and artificial respiration by the two-chamber bellows method invented by Hunter. This bellows produced inspiration by positive pressure and expiration by suction and allowed for an intake of oxygen. However, Kyte's two-chamber bellows of a limited capacity of 500 c.c. soon became standard because of a general feeling that uncontrolled pressure exerted in the lungs might prove injurious. Heat and bellows remained standard for about forty years, or until shortly after Leroy, in 1827, reported disastrous results from the sudden inflation of the lungs in experimental animals. Then the Society withdrew all approval of methods of resuscitation except the application of heat, preferably by immersion in water at 100° F. Keith's tables based on a careful review of the records of the Royal Humane Society of London show that from 1795 to 1811, i.e., within the period of resuscitation by use of heat and bellows, 54.8 per cent of the cases were unsuccessful, whereas from 1832 to 1851, when warmth and friction

alone were used, there were only 10 per cent of cases that were treated unsuccessfully.

The next half century is marked by the presentation of four manual methods of artificial respiration named and reported as follows: The Marshall Hall in 1857, the Sylvester in 1858, the Howard in 1869, the Schaefer prone pressure method in 1903. All these methods received various degrees of recognition by both lay and medical societies in England, on the Continent, and in the United States and Canada. But the Sylvester method from 1862, when it was given preference over the Hall method by the Royal Humane Society, received the greatest support and even as late as 1911 remained practically the only manual method of resuscitation taught in medical schools, and in the great industries. However, in the United States and Canada since 1911 all manual methods have rapidly given way to the Schaefer method, as the direct result of investigations and recommendations made by resuscitation commissions composed of outstanding scientists.

Previous to the investigations of the First Resuscitation Commission, two machines, the pulmotor and the lungmotor, had come into common use by industries, police and fire departments, hospitals and emergency stations. The pulmotor is simply an adaptation of the two chamber bellows of Hunter, whereas the lungmotor is practically identical with the *"pompe apodpinque"* introduced by Courtois in 1790.

However, the Resuscitation Commission charged with the investigation of both manual and mechanical methods of artificial respiration condemned the lungmotor and the pulmotor in the first and in subsequent reports as less effective than the prone pressure method, and as dangerous to the victim.

Practical Considerations.—Schaefer, in experiments in apneic subjects, presented evidence that the prone pressure method gives a greater exchange of air per minute than any of the other manual methods. Polman by use of individuals trained not to interfere with artificial respiration reports in favor of the Sylvester method as against the Schaefer. Lilijenstrand *et al.,* using apneic individuals, state that all manual methods produce a much smaller respiratory exchange than normal and that the Schaefer method produces the least. But Loewy claims that instead of getting relaxation in the production of apnea, one gets a tonus of respiratory muscles which may cause a person to react against artificial respiration more than usual. Polman's experiments are open to the objection that even trained individuals may unconsciously interfere with artificial respiration, particularly when given by the prone pressure method. Lilijenstrand's experiments are open to criticism because they were conducted on individuals in whom apnea was only slight. Henderson, however, produced apnea by over-ventilation of the lungs for two or three minutes, the apnea lasting from forty to eighty seconds. He reports slightly in favor of

the Schaefer method over the Sylvester method, but indicates that both show about half the normal respiratory volume. Meltzer compared results of manual methods in curarized animals, previously anesthetized. This method paralyzes the respiratory muscles as long as the operator wishes. When any method of artificial respiration is ineffective, circulation ceases sooner or later. The Sylvester method sustained circulation for 12 minutes, the Schaefer method for a minimum of 18 minutes, and in one dog for 31 minutes, but so much force was used on this dog that the liver was ruptured. Meltzer concluded that no manual method sustained life for any great length of time and that positive pressure machines were even less effective. He was able by his own apparatus to sustain life for hours. In this experimental work Meltzer applied what after all is the most important standard for the measurement of the efficiency of any type of artificial respiration, namely, "Will it sustain life for a sufficient length of time?" To this should be added, "to allow for the reëstablishment of normal respiration."

There is considerable evidence that in man the respiratory volume may be reduced much below normal and yet be sufficient to sustain life for many hours because of a marked depression of all body functions and activities and a consequent conservation of oxygen. This is well illustrated by skull fracture cases which have recovered after hours of Cheyne-Stokes respiration in which only four or five gasps are taken per minute while the pulse rate drops as low as 40 beats a minute. Another type of case indicates the need for much less ventilation than normal and considerably less than that produced by the prone pressure method; Landry's disease developed to the point at which all respiratory movements have ceased. One case in Chicago, in 1927, was kept alive 108 hours and another in Youngstown, Ohio, in 1928, for thirty-seven hours by moderate manual alternate pressure and release, applied just below the right and left anterior costal margins. To those familiar with methods of artificial respiration it is obvious that the volume of air exchanged by this method is markedly less than normal, or than that produced by the prone pressure method. But more exact evidence of the effectiveness of the Schaefer method in sustaining life appears in two cases of brain tumor reported by Drinker from the records of Cushing. Both these patients stopped breathing and were given artificial respiration by the Schaefer method until normal respiration returned after removal of the tumor. Furthermore, Maclaclen reports a restoration of normal respiration in a victim of electric shock after eight hours of artificial respiration by the Schaefer method. To these selected cases can be added hundreds of other victims of respiratory failure in whom normal respiration has been restored after half an hour to an hour of artificial respiration. This certainly gives ample leeway for the resuscitation of cases of respiratory failure which can be reversed, for the great majority are revived in less than twenty minutes.

Any method of artificial respiration to be of value in electric shock, gas poisoning, and drowning must be simple, effective, as near fool-proof as possible, readily available and easy to apply. No manual method meets all of these requirements except the prone pressure method. No machine has or can ever meet all these requirements for above everything else the great need is for immediate action, since a delay of minutes and even seconds may prove fatal. But the prone pressure method offers additional advantages: (1) It affords ample opportunity for the escape of fluids, and other materials from the mouth as well as from the respiratory tract; (2) it eliminates the need for special care of the tongue; (3) it is less liable to injure the liver or to fracture the ribs.

STANDARD TECHNIC FOR ARTIFICIAL RESPIRATION BY THE PRONE PRESSURE METHOD

The standard technic [1] which is now recommended both in the United States and in Canada, as a result of a conference in Washington in 1927, is as follows:

1: Lay the patient on his belly, one arm extended directly overhead, the other arm bent at the elbow, and with the face turned outward and resting on the hand or forearm so that the nose and mouth are free for breathing (see Fig. 1).

2. Kneel, straddling the patient's thighs with your knees placed at such a distance from the hip bones as will allow you to assume the position shown in Figure 1.

Place the palms of the hands on the small of the back and fingers resting on the ribs, the little finger just touching the lowest rib, with the thumb and fingers in a natural position, and the tips of the fingers just out of sight (see Fig. 1).

3. With arms held straight, swing forward slowly so that the weight of your body is gradually brought to bear upon the patient. The shoulder should be directly over the heel of the hand at the end of the forward swing (see Fig. 2). Do not bend your elbows. This operation should take about two seconds.

4. Now immediately swing backward so as to completely remove the pressure (see Fig. 3). At same time release hands with upward and outward motion.

[1] As a result of many meetings and most careful discussion, this standardized text describing the Schaefer prone pressure method of artificial respiration was recently agreed upon at a meeting held under the auspices of the United States Public Health Service, Washington, D. C., by the following interested organizations: American Gas Association, American Medical Association, American Red Cross, American Telephone & Telegraph Company, American Public Health Association, National Electric Light Association, National Safety Council, United States Army, United States Navy, United States Bureau of Mines, United States Bureau of Standards, United States Public Health Service, and Bethlehem Steel Corporation.

Fig. 1.—The First Position in the Prone Pressure Method of Artificial Respiration.

Fig. 2.—Second Position in the Prone Pressure Method of Artificial Respiration.

Fig. 3.—Third Position in the Prone Pressure Method of Artificial Respiration. The operator waits two seconds then repeats the cycle starting as in Fig. 1.

5. After two seconds, swing forward again. Thus repeat deliberately twelve to fifteen times a minute the double movement of compression and release, a complete respiration in four or five seconds.

6. Continue artificial respiration without interruption until natural breathing is restored, if necessary four hours or longer, or until rigor mortis sets in.

7. As soon as this artificial respiration has been started and while it is being continued, an assistant should loosen any tight clothing about the patient's neck, chest, or waist. Keep the patient warm.

8. To avoid strain on the heart when the patient revives, he should be kept lying down and not allowed to stand or sit up.

9. Resuscitation should be carried on at the nearest possible point to where the patient received his injuries. He should not be moved from this point until he is breathing normally of his own volition and then moved only in a lying position. Should it be necessary, due to extreme weather conditions, etc., to move the patient before he is breathing normally, resuscitation should be carried on during the time that he is being moved.

10. A brief return of natural respiration is not a certain indication for stopping the resuscitation. Not infrequently, the patient, after a temporary recovery of respiration, stops breathing again. The patient must be watched and if natural breathing stops, artificial respiration should be resumed at once.

11. In carrying out resuscitation it may be necessary to change the operator. This change must be made without losing the rhythm of respiration. By this procedure no confusion results at the time of change of operator and a regular rhythm is kept up.

The prone pressure method of artificial respiration described in these rules should be used ·in cases of suspended respiration from all causes (drowning, electric shock, carbon monoxid poisoning, injuries, etc.). Delay of even one minute in the application of the method may lose a life. Follow the instructions even if the patient appears dead. Continue artificial respiration until natural breathing is restored or until rigor mortis has set in. Success has come after eight hours of effort.

The H-H Inhalator (Fig. 4).—In 1920, Henderson and Haggard enlisted the services of the Mine Safety Appliance Company in designing an inhalator which would embody all of the accepted principles for such a device. This company applied the lung-governing principle of the Gibbs reducing valve used in oxygen-breathing apparatus, and with that as a basis developed the H-H Inhalator.[2]

Figure 4 shows a portable carbon dioxid, oxygen inhalator in use in conjunction with artificial respiration. The apparatus consists of a steel

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[2] There are two other inhalators now in use which have received the approval of the Resuscitation Commission.

tank or bottle charged to about 120 atmospheres of oxygen and 6 atmospheres of carbon dioxid, that is 5 per cent, with an allowable variation of 0.5 per cent carbon dioxid. The bottle is connected with the reducing valve, which automatically delivers any quantity of gas that may be drawn at a uniform pressure of about 1.5 pounds per square inch. The gas then passes through the graduated needle valve, which serves both as a control and as a meter for estimating the volume of breathing, so that the supply to the patient can be adjusted to any volume from 0 up to 30 liters a minute. From this needle valve the gas flows into a bag of rubber and cloth of 4 or 5 liters capacity. Beyond this bag is a pair of disk valves

FIG. 4.—PRONE PRESSURE METHOD. ARTIFICIAL RESPIRATION COMBINED WITH INHALATION TREATMENT.

arranged on a T-piece so that the upper one, which has a very light disk, allows the patient to inhale the contents of the bag at the beginning of a respiration, while the lower valve with a heavier disk only opens to admit outside air after the bag has been sucked empty. From the upper disk valve a hose of 0.8 inch bore leads to a snout mask. On the mask is an expiratory valve. This apparatus has been given the name of the H-H Inhalator.

The following sheet of instructions is put into each of the inhalator boxes:

DIRECTIONS IN BRIEF

1. Open valve at top of tank.
2. Put mask on victim.
3. Turn pointer on dial to 10.
4. Keep advancing pointer as victim breathes more.
5. Use for from twenty to thirty minutes.

1. This apparatus is charged with oxygen and another gas (CO_2) which makes the victim breathe many times the amount he otherwise would. It makes him pump the illuminating gas out of himself.

2. If the victim has stopped breathing before you arrive, apply both manual artificial respiration and the H-H Inhalator. If anything will start him breathing, this inhalation will.

3. In using the inhalator, open the valve at the top of the black gas bottle. See that the pointer on the nickel plated dial is turned as nearly as possible to 0.

4. Put the mask over the victim's face. The lower part goes well below the chin. Press down firmly over the nose. Prevent leaks.

5. When the pointer on the nickel plated dial is at 0 the victim breathes air which he draws in through the inlet valve below the T-piece at the end of the long rubber hose.

6. As soon as the mask is on the victim's face, turn the pointer to 10; this lets gas run from the tank into the rubber bag. The victim breathes this. If he breathes more than runs in, the bag collapses and he draws in additional fresh air, through the inlet valve.

7. As the victim's breathing increases, turn the pointer on the dial so as to just keep the bag from collapsing each time he breathes in.

8. If the victim goes well, the breathing will increase to 25 or 30 liters a minute (as shown on the dial) during the first five minutes.

9. Keep the pointer at about 25.

10. Usually twenty minutes of use of the inhalator is all that is necessary but it may be given in severe cases for forty minutes. More than this merely wastes the oxygen $+ CO_2$.

Since 1922, when the Resuscitation Commission reported in favor of the H-H Inhalator, this method of treating gassed cases has been adopted by the important gas companies, by fire and police departments, by mining companies, steel industries, hospitals and emergency stations throughout the United States, Canada and Europe. Thousands of gassed victims have been treated by rescue squads and by physicians, and innumerable reports indicate results that leave practically no question about the value of this treatment. On the basis of these results there is every reason to believe that this treatment is thoroughly sound in practice, and that it affords the gassed victims the best chance for a recovery.

There should be a sufficient number of these machines in every community so that gassed cases may receive treatment within half an hour or less, and every effort should be made by physicians to see that such a machine becomes a part of standard equipment for hospitals.

Other Uses for the Inhalation of Carbon Dioxid, 5 per Cent, or for the Mixture: Oxygen, 95, Carbon Dioxid, 5.—Henderson states that this is the most effective way of removing any volatile poison from the body. The method has been used successfully in the treatment of victims of gasoline fumes, by Hunter and Mudd in cases of acute alcoholic coma and by others in cases of respiratory failure following anesthesia when morphin

has been used prior to its administration; moreover, White has had unusual success in the use of this method for the deëtherization of patients. These findings are confirmed by Sword of the Grace Hospital, New Haven, who had treated up to 1924 more than one hundred cases of all types. He states that it is particularly useful as an adjunct to ethylene anesthesia. In practice Sword says it greatly decreases vomiting, nausea, and gas pains, and reports favorable results in an otherwise uncontrollable postoperative hiccup, and in obstetrical cases after prolonged anesthesia, in which the infant has not breathed spontaneously. Sword also states that arterial pressure is quickly restored to a normal level.

Machines for Producing Artificial Respiration without Positive Pressure Insufflation.—It has already been stated that all positive pressure machines of the lungmotor and pulmotor type have been persistently condemned by the many resuscitation commissions and committees that have investigated the subject of artificial respiration since 1911, on the grounds that they are ineffective and dangerous. But those familiar with the problem realize that there is a decided need for a machine which will give artificial respiration over long periods of time without discomfort or danger to victims who require this treatment such as cases of poliomyelitis, Landry's disease, as well as some cases of drowning and electric shock. Archer has reported a machine by Eisenmenger, which consists of a dome shaped part which is firmly strapped to the chest and abdomen of the patient, and a two-way pump which alternately forces air into the dome and withdraws it. The machine gives excellent ventilation without much discomfort to the patient. Thunberg has developed a machine called the barospirator, which works on an entirely different principle from that used in any other for this type of work. This machine produces no respiratory movements but depends on a good supply of air by pressure ventilation instead of volume ventilation. The patient is placed entirely inside of a horizontally shaped cylinder and ventilation is accomplished by rhythmic pressure differences between the air in the cylinder and the air in the respiratory passages. The lungs become an entirely passive part of the performance and the barospirator chamber the active part. Most patients soon lose all respiratory movements. There are no subjective sensations other than those from ears and there is no possibility of harm.

Drinker has recently developed another type of machine into which the victim is placed, all except the head which remains outside of the cylindrical chamber. Respiratory movements are produced and maintained by the development of alternating negative and positive pressure within the cylinder by use of a two-way pump.

It is evident that such machines will gradually find a place in hospitals to which victims who require prolonged artificial respiration can readily be brought. It is just as evident, that no machine can possibly

take the place of a simple manual method of artificial respiration which can be applied to the victim of respiratory failure immediately.[3]

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CHAPTER XXXI

THE PRESENT STATUS OF INSULIN THERAPY

R. T. Woodyatt

Utilization of glucose is necessary for the preservation of life, and insulin is necessary for the utilization of glucose. Little or no glucose undergoes any type of chemical change in the body in the absence of insulin. Under normal conditions the insulin necessary for the utilization of glucose is elaborated by the insulin-producing glands, and the amount set free in the circulation is automatically regulated to meet variations of the glucose supply. In a sense, therefore, normal individuals are at all times under insulin therapy. In diabetes mellitus the power of the body to produce insulin, and with this its power to regulate the insulin dosage, falls below normal, approaching zero in the most severe cases.

INDICATIONS FOR ARTIFICIAL INSULIN ADMINISTRATION

In the absence of a curative treatment for diabetes the aim of therapy is to prevent or annul any and all disability. When this can be accomplished by diet adjustment, nothing further is required, otherwise supplemental injections of insulin are necessary.

In deciding whether or not in any given case dietary methods will suffice, the following principles should be considered: To avoid disability from undernutrition a patient must have a caloric supply sufficient to maintain a chosen body weight and support normal activities. It is not desirable for a diabetic patient to be fat or abnormally thin. In fixing the weight it is necessary to individualize. Two men of the same height being of different physical types may be most effective at different weights, or the same man doing at one time more physical and at another more mental work may find it desirable to change his weight. In any event, the body weight and amount of activity considered essential for a given case fix the number of calories necessary to avoid any degree of disability from undernutrition. In diets providing 1 to 2 grams of protein per kilogram of body weight daily and in which the proportion of C, P and F are as in the formula $F = 2 C + 0.5 P$, the grams of glucose and the number of calories provided are in the ratio of approximately $1:17$. If then, in a given case, it is deemed necessary for health and efficiency to maintain the body weight at 50 kilograms and allow 35 calories per kilogram per day,

the diet must provide 1750 calories, and if it is decided to construct the diet in accordance with the formula $F = 2 C + 0.5 P$, then the patient will have to utilize some 100 grams of glucose per day. If the urine can be kept normally sugar-free on this diet without artificial insulin doses, the latter will not be necessary. Otherwise it will be necessary either (1) to use insulin or (2) lower the caloric value of the diet or (3) use a diet having a higher fat-carbohydrate ratio. Alternative 2 entails some degree of disability. While there is no serious theoretical objection to 3, nevertheless, apart from theoretical considerations, it may be said that diets based on the formula $F = 2 C + 0.5 P$ contain the proportion of fat in a mixture made up of half milk and half cream and that in actual practice it is difficult to make up diets with more fat, that permit a wide range of agreeable menus and that will be adhered to over long periods of time by the average American patient. In a case of the type presented above, prior to the advent of insulin, if the urine showed sugar, it was customary to eliminate it by undernutrition and to attempt later to build up the diet as the rising glucose tolerance permitted. To-day, with the insulin, a better practice would be to continue the diet of choice and to make the urine sugar-free by supplemental insulin doses. Then if, as the urine is kept sugar-free, the tolerance rises, and the patient begins to show insulin reactions, the dosage may be reduced and finally, in favorable cases, stopped entirely. Meanwhile the patient is taught how to use insulin himself, and if in the future he needs it again, as he will in a large proportion of cases, he need not go through a second hospitalization.

Whereas the above concerns borderline cases in which doubt might exist as to the necessity of insulin therapy, acidosis as indicated by a definitely positive ferric chlorid reaction in the urine with or without characteristic symptoms of acid intoxication presents a positive indication.

ACIDOSIS WITHOUT SYMPTOMS OF ACID POISONING

Any diabetes, no matter how mild, may be aggravated by factors disturbing the even tenor of the patient's physical or emotional life. Traumatism, burns, surgical operations, colds, infections, emotional depression or intercurrent illnesses of any type, etc., may cause an habitually mild diabetes to assume the aspects of a more severe case. Such aggravations are not inevitable, but nevertheless common. Patients should know the possibilities and be trained to observe the urine at short intervals at such times. This applies with especial force to patients already on insulin treatment.

Acidosis should be discovered early before it has time to cause depletion of the alkali reserve of the body or the symptoms of acid intoxication that supervene when the depletion becomes sufficiently marked. When discovered acidosis should always be stopped promptly. Early discovery

depends upon realization of the conditions under which it may develop. A patient whose urine is habitually sugar-free should watch the urine with special care when he has a cold or any illness or vicissitude capable of lowering tolerance. Finding sugar when none was present before, he should also test for acidosis and, finding this, take steps to stop it. The steps taken differ according to the type of the case. A relatively mild non-insulin case may find it sufficient to lower the diet enough to check the glycosuria by methods in vogue before insulin became available. Acidosis may be present even when the urine is normally free of sugar, but, except in the presence of unusual complicating factors, it will not be dangerous in these conditions. In more severe cases and especially all cases who are taking insulin the following program may be adopted:

1. Empty the bladder.

2. Administer a dose of insulin (*i.e.*, 5, 10, 15 or more units depending on circumstances, the size of the initial dose to be discussed below).

3. Give 400 grams of milk or of two parts milk to one part of cream or of half milk and half cream, *i.e.*, a standard easily obtainable and easily measurable feeding that will approximately cover the caloric requirements of the patient for six hours at rest.

4. Collect the urine for the next six hours, closing the first period by emptying the bladder six hours after the first emptying and test the six-hour-specimen for sugar and aceto-acetic acid.

5. Administer a second dose of insulin and again give 400 grams of milk or milk and cream mixture as before. If the urine of the preceding six-hour-period shows sugar and aceto-acetic acid make the second dose of insulin 5 units higher than the first and proceed as before to the close of the second six-hour-period; at that time test again for sugar and acid.

6. If both sugar and acid still persist, again raise the dose of insulin 5 units above the preceding dose, give again the standard feeding and proceed as before.

By following the above program in a case showing acidosis, but without symptoms of acid poisoning, the acidosis and glycosuria will, as a rule, be controlled within twelve to eighteen hours, at the end of which time it will be known exactly how much insulin is necessary for a six-hour period on the standard feeding. Thus, if the dose of insulin given at the beginning of the third period were 20 units and if the urine obtained at the close of this period gave faint or negative qualitative tests for sugar and aceto-acetic acid, it would be evident that for the time being 80 units of insulin per twenty-four hours would be required to keep the urine free of sugar and acid on a diet corresponding to 4 of the quarterly feedings. Naturally, as

soon as the glycosuria and acidosis are under control the requirement for insulin may begin to fall and it is desirable to continue with the six-hourly program until in two successive periods the same dose of insulin proves satisfactory. If during one period an insulin reaction develops, this will call for a lowering of the dose at the beginning of the next, and so on. When stability is established the next step is to restore a 3-meal schedule with 3 instead of 4 doses of insulin. One method of accomplishing this is to multiply the feeding and insulin dose for a single period by 4 and divide by 3. Thus, if in 2 successive periods the patient received 400 grams of the milk-cream mixture and 15 units of insulin per period without insulin reactions or glycosuria, this would be at the rate of 1600 grams of milk and cream and 60 units of insulin per day. One may then try giving 533 (or about 500) grams of milk and cream and 20 units of insulin in the morning, at noon and in the evening, with no feeding or insulin during the night. This will succeed in the not too difficult case. It is then a simple matter to substitute for each feeding of milk and cream a mixed feeding of ordinary foods having approximately the same glucose value and then to combine the noon with the morning dose of insulin, leaving the patient on 3 regular meals and 2 doses of insulin. It is desirable for patients to learn this or some equivalent emergency program and carry it through, taking all the steps at least once or twice. Then, if experience shows that in returning from the six-hourly program to the normal régime some of the steps can be combined, he may be allowed to save time in this way. In some cases, the attempt to pass from the six-hourly back to a normal schedule, as above outlined, will fail, the patient showing sugar and acidosis during the night or early morning. In such cases it may be necessary to continue a small midnight dose of insulin (without a feeding) until altered conditions permit its withdrawal.

ACIDOSIS WITH SYMPTOMS OF ACID POISONING

During continued acidosis, aceto-acetic and beta-hydroxybutyric acids enter the body from endogenous sources at abnormal rates. A part of the acids so introduced may be destroyed by oxidation and a part may appear in the urine unneutralized. The remainder combining with body bases leaves the body as neutral salts, each molecule of acid thus neutralized and excreted carrying out of the body into the urine the base required for its neutralization. Unless this process is counterbalanced by the intake of a sufficient quantity of base to make good the losses, the body content of base must fall, and when it falls below certain levels symptoms of poisoning make their appearance, the character of the symptoms depending primarily on the level reached and the time during which a given level is maintained. With a continuing acidosis causing a continuous fall of the alkali reserve the earliest symptom is commonly weakness. With this there

is commonly breathlessness if the patient exerts, although in the earlier stages the increased frequency and depth of respiration which later characterize the picture may be missed if the patient is resting in bed. Nausea with or without vomiting is a very common early symptom. Abdominal pain or general neuritis-like pains appear in a fairly large percentage of cases. Dulling of the sensations and hyperpnea become more marked as the poisoning deepens and incidentally the pain and nausea, if these were present, tend to subside. Complete coma from which the patient cannot be aroused seldom appears until shortly before death. In nearly all cases careful examination will reveal a flush in the face until the heart begins to fail or recovery sets in.

In the presence of acidosis with any or all of the above symptoms it is practical to conduct therapy by six-hour periods as in acidosis without such symptoms. The primary purpose of therapy is not to lower the blood-sugar percentage or render the urine free of sugar, but to increase the oxidation of sugar in the body as much and as promptly as possible. In cases of acidosis with symptoms of acid intoxication the quantity of insulin necessary to provide for the oxidation of one gram of glucose is very much higher than under ordinary conditions. If the patient receives 1 unit per kilogram of body weight subcutaneously the action curve rises rapidly, remains at its height for about six hours, then rapidly falls. Giving more than 1 unit per kilogram prolongs more than heightens the action curve. In advanced cases, however, it is best to insure maximum effects in the first six hours by giving at once the larger dose, since the loss of even a few hours may place the patient beyond recovery. There is no purpose in giving repeated smaller doses during the first period, to do so implying that the first was insufficient to secure maximum effects and merely confusing the six-hour schedule.

The first step, therefore, is to give a decisive dose of insulin calculated to secure as much insulin effect as can be obtained in the first six hours. Having done this, one may then cleanse the bowel with a simple enema and inject slowly for retention warm normal salt solution in the amount of 5 to 6 c.c. per kilogram of body weight (300 c.c. per 50 kilograms). The condition of the bowel should be preserved for water retention, and anything to irritate the bowel, such as sugar, soda or a Murphy drip, is better avoided. When symptoms of acid poisoning are moderately marked, but not too far advanced, one may expect general improvement with a fall of the rate of respiration in three to five hours, and before this there need be no concern on the score of possible insulin reactions. If in this time the condition is clearing a specimen of urine may be obtained, by catheterization if necessary, and tested qualitatively for sugar and aceto-acetic acid. If the volume of urine is small and the test for sugar not very marked, or if for any reason it is not possible to obtain and test the urine, or if there is any uncertainty in the mind of the attendant as to whether or not the patient is passing

enough sugar to insure against the possibility of an insulin reaction, the patient may be given sugar at the rate of 5 to 10 grams (50 to 100 grams of orange juice) each hour with water sufficient to make the total volume intake by stomach not greater than 5 c.c. per kilogram (250 c.c. per 50 kilograms per hour or 1500 c.c. per 50 kilograms per six hours). Greater volumes of fluid by mouth in advanced cases, especially in children, may lead to acute dilatation of the stomach. Should this or any other obstacle stand in the way of administering by mouth the quantity of sugar necessary to prevent an insulin reaction, *i.e.*, to keep plenty of sugar passing through into the urine, the sugar may be given subcutaneously in the form of a sterile 10 per cent, glucose solution slowly at the rate of 50 to 100 c.c. per hour. Six hours after the initial dose of insulin the bladder should be emptied by catheter if necessary, and the urine tested for sugar and acid. A second dose of insulin is then given to begin the second period.

In choosing the size of the second dose it is preferable to err on the side of giving an unnecessarily large dose rather than take any chances with one that is insufficient to hold, and increase advantages gained in the first period. A common error is to lower the dose too much and allow past symptoms to reappear. This often leads to fatalities as the heart fails under the prolonged acid effects. If the initial dose were 2 units per kilogram and the condition were markedly improved at the end of six hours the second dose might be reduced to 1 unit, which would have virtually the same effect, but more nearly limited to the six-hour period. With progressive improvement, however, the danger of inducing an insulin reaction —which would be highly undesirable in the case of a weakened patient and might prove fatal—is no longer fictitious, so that covering doses of orange juice, 50 to 100 c.c. every hour, or an equivalent hourly administration in some other form are essential. Whether to give 5 or 10 grams of glucose (50 or 100 grams of orange juice) may be determined by examination of the urine at two-hourly intervals. In case of doubt the larger dose is given.

Proceeding in this manner, by the end of one of the periods the case will have been converted from one of acidosis with symptoms of poisoning to one of simple acidosis which can then be managed according to the program outlined above for such cases. In effecting the change from hourly feedings of orange juice or its equivalent to six-hourly feedings of milk, or milk and cream, it may be noted that 6 feedings of 50 (or 100) grams orange juice totaling 300 (or 600) grams for a six-hour period have a glucose value of approximately 30 (or 60) grams. Estimating the glucose value (G) of milk by the formula $G = C + 0.58\,P + 0.1\,F$ we find for 100 grams milk a glucose value of approximately 7 grams and for half and half approximately 8 grams. A feeding of 400 grams of milk or half and half would therefore introduce 28 to 32 grams glucose into the body, corresponding closely with the 6 feedings of 50 grams orange juice. Should

the covering dose of orange juice have been 100 grams per hour, it will be necessary in making the transition to allow for the difference in glucose value by reducing the dose of insulin one half in the first milk and cream period.

MAINTAINING FREEDOM FROM GLYCOSURIA

The practice of keeping the urine sugar-free has for its purpose the conservation or restoration of tolerance. So long as tolerance remains to conserve, or while there is hope that by keeping the urine sugar-free significant tolerance may develop, the practice is rational. But when it becomes evident that the power of the body to produce insulin has sunk permanently to a level so low that to support a nourishing diet it is necessary to administer maximum doses of insulin, it is not imperative to keep the urine sugar-free. If this can be done easily without subjecting the patient to an unduly arduous régime in order to thread his way between glycosuria on the one hand and insulin reactions on the other, it is preferable to do so. Otherwise it is preferable to allow some sugar to pass through the body into the urine, enough to avoid insulin reactions, in which case the ferric chlorid test replaces the test for sugar, the patient being instructed to keep the urine free of aceto-acetic acid. In the case of children with diabetes it is to be expected that if the diet is sufficient to provide for normal growth and development a time will arrive within the first, second or third year of the disease when it will be difficult to keep the urine sugar-free and the patient free of insulin reactions. When this stage is reached it is preferable to avoid undernutrition, acidosis and insulin reactions, but not necessarily glycosuria.

HYPOGLYCEMIC REACTIONS

These vary greatly in character in different cases, so that in some instances the diagnosis may be uncertain. In a patient under insulin treatment the most probable time for a reaction is two to three hours or more after a meal preceded by a dose of insulin. However, patients taking more than 15 to 20 units before breakfast may develop a reaction during the lunch hour, or if the lunch is light, two to three hours later after the absorption of food is ended. With U-10, U-20 or U-40 insulin (in doses up to 40 units), reactions are seldom seen when six to eight hours or more have passed since the dose was given. With U-80 insulin more delayed reactions sometimes occur if the dose is large. Insulin reactions do not occur at a time when the patient is passing sugar in the urine. It is possible, however, for sugar-containing urine to pass into the bladder during the first two to three hours after a meal preceded by insulin and remain there during the following hour or hours in which the urine becomes sugar-free and a reaction develops so that urine obtained from the bladder during the reaction may contain sugar passed into the bladder before the reaction developed.

Insulin reactions always stop promptly when sufficient sugar enters the circulation. In patients in vigorous health they seldom, if ever, prove fatal. Elevation of the pulse is very constant and usually attended by psychic, emotional or nervous symptoms. Sweating, tingling of the skin, trembling or a sensation of trembling, disorientation, lapses of consciousness, slow contractions of the muscles, convulsions, etc., are among the more common symptoms. In cases of doubt as to diagnosis, which may arise especially in cases in which there are complicating arterial, cardiac or central nervous system diseases the fact that the patient is taking insulin, the length of time after the dose that the symptoms appear, the rate of the pulse, the presence or absence of glycosuria and the response to sugar administration, usually serve to settle the question.

SPONTANEOUS HYPOGLYCEMIC REACTION

Undernutrition carried to an extreme may lead to exhaustion of glycogen reserves, a virtual disappearance of the blood-sugar and typical hypoglycemic reactions with convulsions and death. The condition of "trembles" in cattle or men, so-called milk sickness, due to eupatorium poisoning (snakeroot) is associated with hypoglycemia as shown by Barr. Autopsies in cases of the epidemic studied by Jordan and Harris showed very soft livers, and in this condition acetone bodies occur in the urine as shown by Woodyatt. It appears not improbable that the drug destroys the glycogen storing capacity of the liver and that as a result of this, as in the liver extirpations of Mann, the blood-sugar falls, while the absence of sufficient body sugar leads to acidosis as in starvation. Wilder reports a case of typical hypoglycemic reaction due apparently to a carcinoma of the islands of Langerhans with excessive endogenous insulin production, and Pribram has collected the literature and autopsy findings in a number of similar cases. Hypoglycemia of the degree necessary to produce the phenomena seen in insulin reactions is, therefore, not necessarily due in all cases to artificial insulin administration, but may develop spontaneously in the course of diseases which result in general denutrition, in sufficient destruction of liver substance, or in excessive endogenous insulin production. The writer has observed two unpublished cases of individuals in diabetic families, who develop symptoms suggestive of mild insulin reactions with hypoglycemia if they go too long without taking food, suggesting the possibility of hyper-insulinism.

MOUTH-GIVEN SUBSTITUTES FOR INSULIN

Frank's synthalin given by mouth daily causes a slow moderate rise of the glucose utilization that reaches a maximum in two to three days and subsides in two to three days after the drug is stopped. The effect is definite

and of much theoretical importance, but insufficient to warrant the use of the drug as a practical substitute for insulin. Moreover in greater than minimum doses it leads to nausea, and liver necrosis has been reported. Of the many other mouth-given preparations alleged to exercise similar effects none have as yet become established and the great majority are fraudulent.

CHAPTER XXXII

A REDISTRIBUTION OF THE CARBOHYDRATE INTAKE IN THE TREATMENT OF OBESITY

Burgess Gordon

The problem of obesity has been one of interesting speculation and research for many years. Various factors, such as the excessive intake of food, restricted exercise, lowered respiratory quotient, disturbance of the endocrine glands and water metabolism, have been considered. Although these are important influences, it appears that an additional mechanism must be explained before the problem is understood satisfactorily.

A solution of the cause for maintenance of the normal weight under varying conditions and food consumption (DuBois) would be a distinct advance in the study of overnutrition. In addition, if it were possible to establish an accurate classification of obesity, perhaps a source of error would be avoided. The terms exogenous and endogenous, used generally in referring to the type of obesity, are misleading, unless the time of onset, the influence of heredity, habit of living and the choice of foods are clearly understood. This is emphasized in the history of an Italian male, age twenty-six, weight 310 pounds, who started to become overweight at the age of eight. His father at thirty years of age weighed 120 pounds, became prosperous and practiced overeating. His weight increased 85 pounds in two years (at the age of thirty-two years he weighed 205 pounds). The patient had been taught to eat rich foods and was allowed to visit a delicatessen store without restriction. His older brothers, who were indifferent to this privilege and his friends less fortunate financially, grew to manhood without acquiring excessive weight. If obesity in this patient could not be attributed definitely to overeating and the history of his father's gain in weight had not been obtained, it might be concluded from a physical examination that heredity rather than environment was a factor in overnutrition.

The importance of critical study is further emphasized in patients with amenorrhea in whom menstruation returns to normal following a reduction in the body weight. In reviewing the course of events in these cases it may appear that the administration of glandular extracts is unnecessary and perhaps actually harmful.

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Various diets have been advocated for the treatment of obesity. Those of Banting, Oertel, Schweninger and von Noorden have been reviewed by Howard. The effectiveness of these or similar plans depends, no doubt, on the underlying cause of obesity. In addition, perhaps, the ability of the patient to tolerate a reduced caloric intake may influence the results in treatment.

It has been noted that patients on low caloric diets experience fatigue, hunger, nervousness and weakness. These hypoglycemia-like symptoms, aggravated during exercise, may be relieved by the administration of readily available carbohydrate. Do the potentially obese start to eat an excessive amount of carbohydrate from habit or a natural desire for food and then continue to practice overeating because transient hyperinsulinism or some other disturbance in carbohydrate metabolism has occurred? This hypothesis was considered in suggesting a plan of treatment for obesity (Gordon and Nissler). The regimen is as follows: The patient tabulates accurately for three days the occurrence of symptoms, the extent of exercise and the amount and type of food consumed (Diet-Symptom Chart). On the fourth day, if there is no contra-indication to a loss of weight, a 1200 to 1400 calorie diet, consisting of 3 to 5 per cent vegetables, 2 to 3 pieces of bread and butter, 100 grams of meat, clear soup, 2 small potatoes, 2 glasses of milk and 1 orange is prescribed. The patient's activities and symptoms are recorded as usual on the diet-symptom chart. On the fifth day the moderately restricted diet is continued, but in addition readily available carbohydrate (dextrose 2 grams) in the form of lozenges, candy or powder are administered every half hour from 9.30 to 11 A.M., 2.30 to 5.30 P.M. and 8.30 to 9.30 P.M. (breakfast, 7.30 A.M.; luncheon, 12.15 P.M.; supper, 6.15 P.M.). On the sixth day the intake of bread is either discontinued or reduced to one-half slice daily and the half-hourly dosage of dextrose is increased from 2 to 4 grams at 10.30 A.M. and 3.00 and 3.30 P.M., or at other times, to relieve symptoms of fatigue, hunger, nervousness or weakness. The patients are urged to walk 1 kilometer (3280 feet) leisurely in the morning or afternoon at the beginning of the diet. The distance is increased gradually, until at the end of two weeks 4 kilometers (2½ miles) are covered daily. The regimen is discontinued after one month and a moderately restricted diet (1400 to 1800 calories) is prescribed. If a further loss of weight is desired the diet is resumed after a rest period of two to three weeks.

The diet plan has been effective in reducing the weight of patients who have an abnormal craving for carbohydrate. So far as determined there have been no untoward effects other than transient headaches at the beginning of the diet, constipation and sensation of fullness in the stomach if the dosage of dextrose is excessive. It is noteworthy, perhaps, that the regimen apparently causes no mental depression and that the craving for carbohydrate usually disappears. Since obesity is regarded usually as a

DIET-SYMPTOM CHART * (JEFFERSON HOSPITAL)

	A.M.						P.M.											
NAME							DATE											
	7 -	- 8 - 9 - 10 - 11 - 12 -					- 1 - 2 - 3 - 4 - 5 - 6 -						7 - 8 - 9 - 10 - 11 - 12					
1 HOUR																		
2 WATER																		
2 FOOD	*Breakfast: approximately 200 calories*						*Luncheon: approximately 600 calories*						*Supper: approximately 500 calories*					
HUNGER																		
WEAKNESS	>	>																
FATIGUE																		
DROWSINESS																		
NERVOUSNESS																		
PERSPIRATION																		
STRENGTH																		
3 DEXTROSE	1 1 2 2 1						1 2 1 2 1 1						1 1 1					
4 EXERCISE	2 4						6 4						3					
WEIGHT																		

NOTES; 1 List activities and symptoms under hour at which they occur.
    2 Give in detail amount of food and water at each meal and between meals.
    3 Record number of dextrose candies and lozenges.
    4 State exercise in blocks covered.

State impression of the effect of the diet upon general condition.
Hours of sleep on previous night.
Specimen of urine collected (hour).

* A tabulation to show the occurrence of symptoms in an obese individual and the management of the dextrose-moderately restricted starch régime. In addition to the routine administration of dextrose (one lozenge every half hour from 9 to 11 A.M., etc.) the dosage was increased at 10 and 10.30 A.M. when symptoms of hunger and weakness occurred. Between 3 and 4 P.M. the dosage of dextrose was also increased in anticipation of symptoms noted on the previous day. This patient had consumed cake, bread and macaroni in large quantities at meal times and between meals. In the diet, these foods were omitted between meals and reduced in quantity (one-third) at meal time.

pathologic state, treatment is continued only under close supervision. A physical examination, including a careful study of the urine, is made at frequent intervals. If there are signs of impending untoward effects, the diet is modified or immediately discontinued. As the danger of rapid loss of weight is appreciated, no patient, unless extremely obese, is permitted to lose more than 2 kilograms (4.4 pounds) weekly.

Although the diet was intended primarily for the treatment of over-nutrition, uncomplicated by other disorders, it has been found of value in treating symptoms in hypertension and failure of the circulation. A striking reduction of blood-pressure and general improvement in the action of the heart have been noted in a few patients who consumed an excessive amount of starch daily.

The chief points of the diet are the reduction in the intake of potatoes and all foods derived from grains (approximately one-third of the former amount consumed at meal time is permitted) and the administration between meals of divided doses of dextrose. No change is made in the customary intake of fat, protein or water. Although certain foods may be suggested, it is usually unnecessary and often unwise to change the varieties which appeal to the patient. For example, the patient may desire, for luncheon, vegetable soup, three small potatoes, tomato and lettuce salad, two lamb chops, six pieces of bread, butter, coffee, and ice cream. According to the regimen the amount of bread would be reduced to two slices and one potato would be allowed; one or two 3 to 5 per cent vegetables may be taken if desired. Since dextrose (10 grams) is administered between luncheon and supper and the vegetables are increased, there is no considerable reduction in the total number of calories as compared with the intake before the diet was instituted.

Dextrose was selected for administration because it was considered a readily available carbohydrate and not likely to cause gastric distress. The candy is manufactured according to the following formula: 1000 grains of dextrose (Corn Products Refining Co.), 250 c.c. of honey, 60 grams of butter and 500 c.c. of water are cooked rapidly. When a temperature of 278° F. is reached the cooking is stopped. During the entire cooking the sugar is stirred vigorously. The mixture is then poured on a marble slab, flavored (peppermint, lime, raspberry, orange, vanilla or chocolate obtained from cocoa shells) and then made into taffy in the usual manner. The candy is rolled and cut into pieces weighing 4 grams (each piece contains about 2 grams dextrose) and wrapped in waxed paper. Dextrose lozenges weighing 2 grams are made by simple compression, no ingredients being used other than flavoring extracts (peppermint, wintergreen or lemon).

Dextrose powder, as a matter of economy or convenience, may be divided in papers (one teaspoonful representing about 2 grams) or dissolved in lemon or orange juice.

Obviously, the hypothesis suggesting that obesity may result from the excessive intake of carbohydrate and a disturbance of the sugar regulating mechanism is largely speculative. It is unproved also that a redistribution of the customary intake of carbohydrate and the administration of dextrose in divided doses restores the disturbed mechanism to normal. It seems likely, however, that patients who experience hypoglycemia-like symptoms require a readily available fuel. If it is true that the glycogen reserve is replenished following the intake of dextrose the amount of carbohydrate, as derived from grains, may be reduced without decreasing the efficiency of physical effort or causing discomfort to the patient. Weight may be lost because the caloric intake at meal time is insufficient for maintenance of excessive fat. Dextrose administered between meals is used chiefly to provide energy.

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CHAPTER XXXIII

IODIN IN THE TREATMENT OF THYROID DISEASES

David Marine

Iodin was first knowingly used in the treatment of goiter by Coindet (1820), although it had been used unknowingly, in sea salt, in mineral waters, in sponge ash, and in various seaweeds, in the treatment of goiter since the earliest times. Within a year after its introduction as a remedy against goiter, Coindet, in 1821, observed injurious effects in certain cases. These effects were vividly and briefly summarized by Gairdner, in 1824, who noted that "peculiar, great and persevering anxiety, depression of spirits, emaciation, diarrhea, tremor and nervous excitement simulating chorea" were produced in certain individuals by the administration of iodin. The empiric use of iodin in the treatment of thyroid diseases continued down to 1895, when Baumann discovered that this element was a normal constituent of the thyroid. Since then there has accumulated a great mass of physiological and chemical facts concerning the function of the thyroid gland and the relation of iodin to it. It is from this knowledge that a beginning has been made in the more rational use of iodin in diseases of the thyroid, although much remains unsolved.

All the knowledge we have indicates that extremely small amounts of iodin are required for the normal function of the thyroid. Thus the maximum storage capacity of the normal human thyroid is about 25 milligrams (⅖ grain). One milligram of iodin given by mouth once a week will prevent thyroid enlargement in dogs living under conditions which would otherwise produce goiter. As shown by Kendall, the physiologically active iodin is contained in a specific chemical group which he isolated and named "thyroxin." The observations of Plummer and Boothby would indicate that the thyroxin requirement of the average normal adult is less than 1 milligram (0.3-0.7 milligram) per day. The average iodin store of the thyroid is about 0.04 per cent fresh weight, or 0.2 per cent dry weight, and it has been shown that when the iodin store is maintained above 0.1 per cent dry weight, no enlargement of the gland occurs. The application of these facts regarding the relation of iodin to thyroid activity has materially helped in reducing the amount of iodin administered and to some extent the injurious effects so frequently noted during the empiric stage.

From the standpoint of iodin therapy the diseases of the thyroid may be grouped as follows:

I. Thyroid insufficiencies
   1. Simple goiter (endemic, sporadic, epidemic)
   2. Myxedema
      (*a*) Of adults (Gull's disease)
      (*b*) Of infants (cretinism)
II. Exophthalmic goiter.

In discussing the use of iodin in the control of thyroid diseases, it is necessary in the first place to distinguish sharply between simple goiter and exophthalmic goiter, and in the second place to distinguish between the use of iodin in prevention and in treatment.

Simple goiter is a work hypertrophy of the thyroid gland. It is the anatomical expression of the inability of the gland to meet the physiological demands of the organism for thyroxin and, therefore, appears to be dependent *immediately* upon a relative or an absolute deficiency of iodin. The remote, predisposing or fundamental causes of the iodin deficiency are for the most part still unknown. It is known that the thyroid will enlarge when the intake of iodin is below the normal body needs or when the body needs for one reason or another are so increased that the usual intake is for the time insufficient. The former condition is seen more particularly in the endemic goiter districts of the world, although it can be experimentally reproduced anywhere, while the latter is seen in the so-called sporadic goiter occurring in association with adolescence, infectious diseases, pregnancy, abnormal diets and certain derangements of internal secretions (Addison's disease, acromegaly, chlorosis, Graves' disease). The association of goiter with such a variety of disturbances in metabolism indicates that the relative iodin deficiencies depend upon a derangement of the balance of other glands of internal secretion which influences the thyroid by inhibiting or neutralizing the action of its hormone.

There is abundant evidence that the sex glands (suprarenal cortex, and the interstitial cells of the ovary and testis) exert an important influence on the thyroid as indicated by the relation of thyroid enlargements to sex and sexual states. If the suprarenal cortex and interstitial cells of the gonads produce a metabolism inhibiting substance, as I believe they do, then there exists a delicate balance which could be upset either by changes in the amount of thyroxin produced and excreted from the thyroid or by changes in the amount of the inhibiting substances produced and excreted from the gonadal tissues. Then in addition, if some essential constituent of the gonadal substance was acquired in highly variable amounts from food and water as is the case with an essential constituent (iodin) of thyroxin, we would have a rational conception of how the relative iodin deficiencies created by such apparently diverse conditions as foods (liver), infections, puberty, status lymphaticus and Graves' disease could be brought about.

Iodin in the Prevention of Goiter.—Simple goiter of the endemic type may be prevented in man by the administration of 1 milligram, and probably less, of iodin daily. Iodin in any form and administered in any manner appears to be effective. The amount of iodin necessary and the ideal plan of administration for this purpose are still undetermined, but from the data available the amount would appear to lie between a minimum of 1 milligram per week and a maximum of 1 milligram per day. The most practical and universally applicable method of providing these amounts of iodin is by means of salt. In Switzerland, Austria, Italy, and New Zealand iodized salt contains one part of potassium iodid to 200,000 parts of salt (0.0005 per cent) in addition to that naturally present; while in America iodized salt contains one part of potassium iodid per 100,000 parts of salt (0.001 per cent) additional. Practically all common salt contains iodin and the traces of iodin added to the iodized salts may be less than that of the original salt.

The use of iodized salt is advisable when universal prophylaxis is desired. Where small groups or units of population are to be protected, as for example school children, starch-iodin or iodostarin tablets containing 5 to 10 milligrams of iodin and administered once a week may be used. Where individuals are to be protected, as for example women during pregnancy or children of a family, almost any dilute preparation of iodin will suffice. Cod-liver oil in doses of 5 to 10 c.c. daily for a month and repeated each autumn and spring would supply sufficient iodin. Also syrup of hydriodic acid or syrup of ferrous iodid in 1 to 2 c.c. doses daily for two to four weeks each autumn and spring is sufficient.

The dangers from the use of such amounts of iodin are negligible. It is possible that certain cases of active Graves' disease might be made worse by the amount of iodin they could obtain from iodized salt but all the cases of "iodin Basedow's" that I have investigated had been taking iodin in other forms in large amounts. Desiccated thyroid would be an ideal drug for the prevention of goiter if it could be used in small enough doses.

Iodin is most effective in the prevention of endemic goiter, that is, where there is a real iodin deficiency. Where the deficiency is relative, that is, in conditions producing an increased demand for thyroid activity, prevention is less successful.

Iodin in the Treatment of Simple Goiter.—As above mentioned, treatment is distinguished from prevention. The patient should be under the care of a physician and not only will be taking larger amounts of iodin than for prevention but should be given desiccated thyroid as well. The relatively small doses of iodin recommended for prevention often have considerable curative effects in endemic goiter when the administration of iodin is begun during the early developmental stages of goiter (Marine and Kimball, Klinger).

Iodin is most effective in the parenchymatous or hyperplastic stage and is much more effective in the treatment of goiter in the lower animals than in man. The reason for this is not entirely clear. In both man and the lower animals iodin is stored rapidly in the thyroid and to about the same extent. Iodin produces involution in both. The great difference is in the degree of shrinkage of the thyroid and this is dependent upon a difference in the amount of colloid stored. Iodin causes the follicles to become distended with colloid material and they do not undergo subsequent shrinkage in man as readily or as rapidly as in the lower animals. The sudden administration of large doses of iodin in human goiter usually causes very rapid distention of the follicles with colloid and in from seven to ten days the gland may become very firm and painful to the touch and clinically even larger than before iodin was administered. This is the so-called "iodin thyroiditis" of the older literature.

In long standing cases of goiter no plan of iodin therapy will do more than relieve any existing thyroid insufficiency. This it does. Occasionally, however, striking curative effects are noted even in long standing cases. In such individuals the thyroid is usually either in the hyperplastic or simple colloid stage, free from adenomata, hemorrhage, cyst, calcification or other degenerative changes so characteristic of long standing human goiter.

Whether a curative effect is produced or not, and particularly if the individual intends to seek surgical treatment in the event of failure, iodin should be given. In the long standing goiters the functional insufficiency has usually been relieved or outgrown and the patient seeks advice largely for the removal of the cervical deformity.

The best plan of medical treatment is to begin with desiccated thyroid for the reason above mentioned, that iodin stimulates the storage of colloid and thus tends to prevent shrinkage. It is best to start with 0.1 gram desiccated thyroid daily for the first week. If this dose is well borne it may be increased to 0.2 gram daily during the second week and if after examination there is no change in the pulse rate, body weight or other evidence of thyroid action, 0.2 gram daily may be continued for another two weeks. Thyroxin has no advantage and many disadvantages over desiccated thyroid in the medical treatment of simple goiter. It is then best to stop all treatment for one to two weeks in order to allow the maximum reduction in the thyroid to occur. Iodin should then be administered in doses of 10 to 20 milligrams daily for the next two or three weeks. This will cause a great increase in the iodin store in the thyroid. Syrup of hydriodic acid if given in 1 to 2 c.c. doses daily will supply the above amounts of iodin. Any other form of iodin is probably as effective, but the tendency is always to give too much iodin. It is only on this account that tincture of iodin, Lugol's solution or solutions of potassium iodid and sodium iodid are less desirable. This combined treatment with desiccated

thyroid followed by small doses of iodin may be repeated three or four times during the year and for the maximum reduction in man at least a year is required. The external application of iodin or its salts should be condemned.

With such doses of desiccated thyroid and iodin very little in the way of untoward effects can occur and if they do, their onset is gradual and detectable before any harm is done. No frank case of exophthalmic goiter should be given iodin or thyroid in these doses.

Iodin in the Treatment of Exophthalmic Goiter.—It is believed that the excessive activity of the thyroid in exophthalmic goiter is secondary to some powerful systemic stimulus concerning the nature of which we are still ignorant. There is some evidence, however, that the thyroid stimulation is in part due to the lack or partial loss of an inhibitory control normally exerted by some substance in the suprarenal cortex and interstitial cells of the gonads. Until the cause of this stimulation is discovered and relieved, no permanent benefit is likely to result from supplying the element (iodin) from which the thyroid can produce and excrete a larger amount of thyroxin more easily and more quickly.

Iodin apparently has the same thyroid effect in both simple goiter and exophthalmic goiter, and it seems to me that the fact that iodin will cure and prevent simple goiter while it has no such effect on the symptom-complex of exophthalmic goiter, offers additional proof that the two diseases are quite distinct.

Exophthalmic goiter patients are hypersensitive to iodin, as they are to most other drugs. The beneficial effects of iodin are limited while its injurious effects are serious. These injurious effects, as already noted, were known to Coindet (1821), and Gairdner, in 1824, vividly described these untoward effects in certain cases of goiter at least eleven years before Graves recognized this syndrome. Some cases of exophthalmic goiter are notably improved by the prolonged use of small doses of iodin; in others the clinical manifestations may remain unchanged but on the whole exophthalmic goiter cases have been made worse by the use of iodin. As shown by Lenhart and Marine, in 1911, iodin brings about a rapid storage of this element and causes involution of the thyroid in cases of Graves' disease just as it does in thyroid hyperplasias of other clinical associations, although less rapid. Iodin appears to be useful in the treatment of exophthalmic goiter in two ways: (1) When given in minute doses as a part of medical treatment, and (2) when given in large doses as a preparatory measure for thyroidectomy.

When used as part of medical treatment the dose should not exceed 1 milligram daily. Mellanby has suggested the use of cod-liver oil in doses up to 15 c.c. daily as a means of supplying traces of iodin. Iodized salt (containing 0.001 per cent iodin) if used as the only source of iodin,

would also supply sufficient iodin. All cases of Graves' disease getting these small doses of iodin should be under the daily observation of a physician for a period of two weeks or until the effect of such doses may be determined. If beneficial effects are noted these small doses may be continued for one or three months when complete involution of the thyroid to its colloid phase will have occurred. As pointed out by Marine and Lenhart, in 1911, where iodin involution has been induced the risk of the operation for thyroidectomy is greatly reduced irrespective of whether there was apparent clinical improvement or not.

The effect of large doses in immediately, though temporarily, improving the clinical appearance of cases of exophthalmic goiter was known to Trousseau (1867), to Cheadle (1869), and many others. Loewy and Zondek, in 1921, observed that this improvement was associated with a decrease in the metabolic rate. Plummer and Boothby, in 1924, introduced the use of large doses of iodin (Lugol's solution, 0.3 to 1.0 c.c. two or three times daily) as a routine preoperative measure and showed that a great reduction in the metabolic rate occurred in the majority of cases with hyperplastic thyroids (that is, previously untreated with iodin). Its use in preparing patients for operation has greatly reduced the operative mortality. The way in which iodin brings about a temporary lowering of the pulse and metabolic rates is still in dispute. The most probable explanation appears to be that rapid storage of iodin and colloid in the thyroid follicles produces stretching and distention and causes a partial occlusion of the perifollicular capillaries and a pressure retention results which temporarily reduces the excretion of thyroxin until the thyroid cells have accommodated themselves to function under the increased pressure. The effect of iodin administration in preventing exhaustion crises and in lowering the operative mortality does not necessarily parallel its effect in lowering the metabolic rate, which suggests that in some quite unknown way iodin also raises the resistance in cases of exophthalmic goiter just as it does in cases of status lymphaticus, and there is abundant evidence that the two conditions are closely related. Iodin in large doses should be used only in cases to be operated upon within two weeks after its administration is begun (Goetsch, 1927). The use of large doses of iodin unfortunately has not been thus limited or controlled, and great harm has resulted, particularly during the past five years, despite the warnings and experience of more than one hundred years.

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[1] The Journal of Physiology uses Roman numerals to indicate pages of the *Proceedings*. This is done to distinguish the *Proceedings of the Physiological Society* from the *Journal of Physiology*, since both are published together.

CHAPTER XXXIV

TREATMENT OF PERNICIOUS ANEMIA

George R. Minot

There is only one essential requirement for the successful treatment of pernicious (Addison's) anemia, namely, that the patient ingest daily an adequate amount of potent material contained in liver in very small amounts, and continue indefinitely to take it with regularity. This effective material, which acts in a specific manner, may be supplied by feeding cooked or raw mammalian liver, or kidney, or potent extracts of liver. Cod fish, salmon and chicken livers also appear to contain the active principle, which perhaps occurs in other organs or foods.

Minot and Murphy's original demonstration that this treatment can promptly, rapidly and with regularity benefit strikingly the health of essentially all patients with pernicious anemia and permit their red blood-corpuscles to return to approximately normal numbers, has now been confirmed by numerous other physicians. Not only have the patients responded promptly to liver therapy, but if they have continued with it satisfactorily, and complications, as infectious processes, have not arisen, their red blood-cells have remained elevated above 4 million and usually above 4.5 million per cubic millimeter. There are records available for fifty cases treated by Minot and Murphy for between two and four and one-half years, and their average red blood-cell count is now (June-July, 1928) 4.75 million per cubic millimeter.

After experience had been gained in the treatment of pernicious anemia by means of liver, the question arose concerning the nature of the material effective in this disease. Although studies pursued have not led to the isolation of the active principle, the chemical fractionation of liver by Edwin J. Cohn and our studies with him indicate that it is presumably a nitrogenous base, which acts to promote the growth of the primitive red blood-cells that crowd the bone-marrow of pernicious anemia in relapse. These studies have led to the extraction from liver of fractions containing the antipernicious anemia substance which have simplified treatment. Only a few tenths of a gram a day constitute an adequate amount of the purest fraction so far fed to produce a prompt response. Extracts for commercial use have been readily prepared, which produce maximal responses when about 15 grams are fed daily, or the amount derived from 500 grams of whole liver (Minot, Cohn, Murphy,

and Lawson). The extract which at present has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association is known as "Liver extract No. 343" (*J. Am. M. Ass.*, 1928, 90:385). This standardized product resembles "Fraction G" isolated while attempting to learn the nature of the effective material, and is manufactured under the direction of the Committee on Pernicious Anemia of the Harvard Medical School. At the present time other excellent extracts of similar nature have been manufactured in the United States of America and abroad, but there are liver extracts for pernicious anemia on the market that are at least weak in potency, and different samples of some products vary greatly in strength. Advantageous changes in the character and strengths of the commercial extracts are reasonable to expect in the future.

Proper liver therapy necessitates prescribing optimal amounts of active principle. At present, the only way to determine whether or not an extract is potent is by testing its effect upon a patient with undoubted pernicious anemia. In pernicious anemia in relapse, except under rare circumstances, there occurs with extraordinary regularity and promptness, as the result of feeding sufficient potent material, a temporary, but large increase of the reticulocytes (young red blood-corpuscles containing material staining vitally with brilliant cresyl blue and certain other dyes—cells intermediate between nucleated and adult erythrocytes). This reaction permits one to tell within about ten days whether suitable material has been fed, and gives considerable information concerning whether maximal amounts have been given or not. The rate of the red blood-corpuscles increase within a month gives similar knowledge.

The reaction of the reticulocytes was discussed in detail by Minot, Murphy, Cohn, and Lawson in 1928. (See references.) The response of the reticulocytes is of the same character when liver, kidney or liver extract is fed. Typical responses of these young red blood-cells are illustrated in Figure 1. The increase of the reticulocytes varies in a fairly regular manner with the level of the red blood-cell count when treatment is commenced and with the amount of potent material administered. Variations also occur dependent upon the precise state of the patient, but these are seldom of importance. Figure 2 shows the influence of feeding standardized extract in essentially maximal amounts to a series of patients. This figure demonstrates the inverse relation between the percentage of reticulocytes in the blood at the peak of their rise and the concentration of erythrocytes before treatment was commenced. Cases with more than 3 million red blood-cells per cubic millimeter never exhibit more than a slight response of the reticulocytes. In essentially all cases, however, treated with adequate amounts of active principle, the red blood-cells rapidly increase to normal.

If a patient with pernicious anemia is given untested material and

there follows directly a reticulocyte response, it indicates the presence of the active principle, although the remote possibility of a "spontaneous" reticulocyte rise at the precise time that one is expected from the substance administered must not be overlooked. If no response of the reticulocytes occurs it is exceedingly probable that the substance fed is inert if the erythrocytes are less than 3 million per cubic millimeter. Thus, under such circumstances, failure to respond to potent material makes it exceedingly
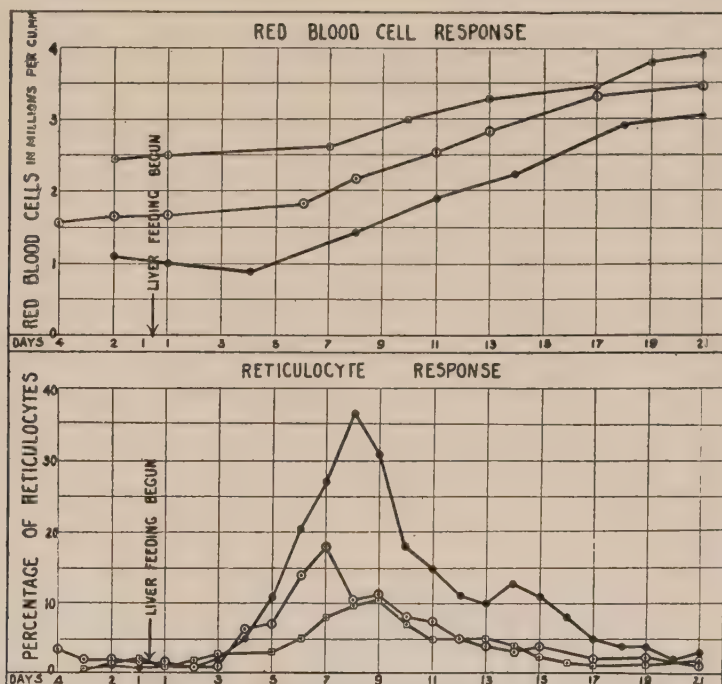
FIG. 1.—THE EFFECT ON THE RETICULOCYTES IN PERNICIOUS ANEMIA OF FEEDING DAILY 220 GRAMS OF LIVER PULP TO EACH OF THREE PATIENTS WITH DIFFERENT RED BLOOD-CELL LEVELS.

The same type of line in each part of the figure records data for the same patient. In general, the highest blood-cell count is accompanied by the lowest reticulocyte count and *vice versa*. (From *Am. J. M. Sc.*, Philadelphia.)

improbable that the patient has pernicious anemia. The presence or absence of the response does not determine the degree of potency of the substance fed, but the maximal numbers of the reticulocytes that appear and the rate of their increase gives useful information concerning this. If the reticulocytes at the peak of their rise fall below the level for comparable cases recorded in Figure 2 the amount of material given did not constitute in all probability a maximal dose.

The feeding of submaximal amounts of active principle may cause variations in the reticulocyte reactions. Serious complications, as severe

septic infections, may do the same. If treatment is commenced when there is a considerable spontaneous increase of reticulocytes, or when this has recently occurred, no subsequent rise may follow liver therapy, or the rise may be less than if the reticulocytes had not been recently increased. The rate at which the reticulocytes reach the peak of their rise is influenced in a measure by the amount of the potent material given and the level of the erythrocytes. The rise is usually more rapid when the red blood-cells are few and the reticulocyte peak occurs sooner when, up to a maximum,
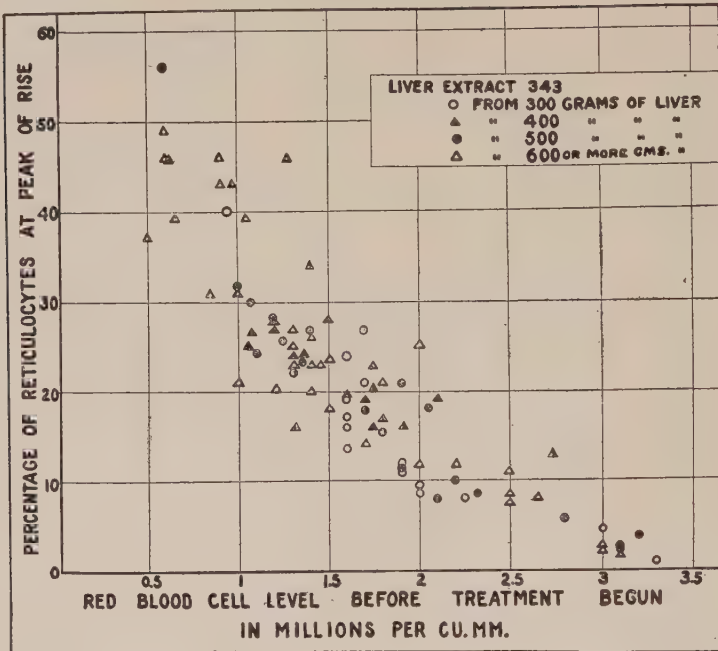
FIG. 2.—THE RESPONSE OF THE RETICULOCYTES TO THE DAILY FEEDING OF LIVER EXTRACT No. 343 (N.N.R.) IN 89 CASES OF PERNICIOUS ANEMIA. (From *Am. J. M. Sc.*, Philadelphia.)

large rather than small amounts of potent material are fed. Rarely, however, will the peak of the reticulocyte rise occur as soon as the fifth day after treatment is commenced and when it is reached after the tenth day the dose of the effective material was probably considerably less than a maximal amount.

Observations on the course of the reticulocytes thus aid to determine the potency of a given preparation and the amount of material to be fed. Experience has shown that when complications are not present maximal increases of reticulocytes and erythrocytes will be obtained when standardized extract derived from 500 or 600 grams of liver are fed daily and apparently when about 250 grams a day of prepared raw liver pulp or

cooked liver are taken.[1] The response perhaps may be hastened by feeding larger amounts over a shorter period of time. In apparently similar cases treated with the same amount of active principle a certain variation occurs in the magnitude of the reticulocyte response. This variation is probably to be attributed to the exact state of the bone-marrow. In some instances there are many primitive cells to be transformed; in others the bone-marrow may not be sufficiently pathologic to allow more reticulocytes to enter the blood-stream even if more active principle were given. Apparently in many cases the amount of active principle contained in standardized extract derived from 300 grams of liver is enough to cause the maximal reticulocyte response, although in others a similar amount may not produce the greatest possible response. This quantity is sufficient to produce satisfactory improvement in many cases and smaller amounts —even 125 grams a day of prepared liver—have benefited strikingly many patients without producing a maximal reticulocyte response. The outstanding difference between the daily use of the extract from 300 or 600 grams of liver tends to affect the rates at which the reticulocyte and total erythrocyte response occur rather than their magnitude.

At the time of the peak of the reticulocyte rise the increased concentration of the erythrocytes is almost wholly attributable to reticulocytes. As they decrease the mature cells continue to increase to normal. There is a direct relationship between the velocity at which the red blood-cells increase and the amount of potent material given, up to a maximum. Their rate of manufacture is slower when their count is above 2.5 million per cubic millimeter. When liver extract derived from 500 or 600 grams of liver and when 250 grams of prepared liver are fed daily to patients with less than 2 million red blood-corpuscles per cubic millimeter, the concentration of these cells will increase on the average about 2.5 million per cubic millimeter in thirty days. After two months of adequate therapy counts in the vicinity of 5 million per cubic millimeter are to be expected.

The daily feeding of the amount of potent material contained in extract derived from 300 grams of liver will increase the erythrocytes more slowly, but the daily administration of only 150 grams of prepared liver may be expected to increase the cells about 1.5 million in thirty days when the initial count is less than 2 million per cubic millimeter. When maximal amounts of the active principle are fed to patients with counts between 2.5 and 3.1 million per cubic millimeter, the red blood-cells sometimes

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[1] When liver or kidney has been fed the amount given has been recorded as that of the prepared organ. This weight is as a rule about 25 per cent less than the weight of the food as bought, but there is considerable variation. Losses are experienced in the extraction of the active principle, although they probably do not exceed 30 per cent. Thus, in comparing figures for weights of liver as purchased, one should add at least 25 per cent to those for prepared organs and deduct about this same amount from the figures for the weights of liver from which extract is derived in order to obtain roughly comparable data.

increase in a month a little over 2 million, but usually about 1.5 million per cubic millimeter.

The necessity for prolonged continuation of liver therapy is emphasized. The chief cause for significant decreases in the red blood-cells after they have once reached normal has been the omission of the ingestion of an adequate amount of liver, kidney, or liver extract. Upon resumption of a suitable amount the count will rise again. Omission of liver, or its equivalent, does not imply that the count will soon fall, for patients may continue without it for months before a decrease of the erythrocytes takes place. The suitable daily maintenance dose apparently varies for different patients. The amount of active principle contained in 300 grams of standardized extract is sufficient in many cases. Proper blood examinations and clinical observations should be made from time to time to determine the amount of material which the patient should continue to take. Red blood-cell counts in the vicinity of 6 million per cubic millimeter have occurred as the result of liver therapy. It is as desirable to avoid unnecessary strain upon the bone-marrow as to prevent the recurrence of symptoms and anemia. Thus, sometimes the amount of active principle formerly prescribed should be curtailed.

An infectious process and complications, such as cirrhosis of the liver and injury of the bone-marrow from multiple transfusions of blood, may retard and decrease the response of the reticulocytes and erythrocytes. Infections are also important causes for decreases of the erythrocytes after their numbers have become normal. Under such circumstances large doses of the active principle should be prescribed. Even if there is little or no anemia and there is a recurrence of symptoms of the disease, such as glossitis, or progression of neurological disorders, the amount of liver, or its equivalent, should be increased.

In spite of the value of the effective fraction of liver, the feeding of liver or kidney remains an important method of therapy. The use of liver extract simplifies treatment, particularly for very ill persons. The powdered extract is readily soluble in water, orange juice or any other acceptable vehicle and may be given in one or more doses a day. It also may be administered in capsules.

It is more difficult to commence treatment with liver itself, but giving little other food soon permits patients to be able to take daily 200 or more grams of prepared liver. If necessary liver or liver extract may be given through a stomach tube. Sympathy, persuasion, and the art of fine cooking and serving, with the assistance of a competent dietitian, will facilitate having the individual take the food desired for him.

Liver may be served in any form that the patient wishes, but prolonged boiling and overcooking are to be avoided. The form of cooked liver most generally preferred is broiled. Receipts for preparing liver dishes are described by Irwin, Nicholls, and Tubbs and Bellinger.

It is difficult for sick persons to eat large amounts of solid liver, but if raw liver pulp or juice, or soup, is given there seldom arises a serious problem about the administration of liver. Two hundred grams of prepared raw liver pulp a day are usually taken readily.

Raw liver pulp may be prepared as follows: Remove the coarser parts of the liver and put the remainder through a vegetable or meat grinder several times, using the finest attachment. Strain through a coarse sieve, then weigh out the amount of pulp for the daily portion and add enough cold water to make it the consistency of heavy cream. Beat with an egg beater and serve ice cold, flavored with orange juice or other ingredients as desired.

The juice pressed from raw liver or a concentrated salt solution extract and liver broth are efficacious, but usually 500 grams of liver as purchased must be utilized to obtain a suitable daily dose. There has been no evidence of infection from parasites from the use of raw liver and this possibility seems remote in the temperate zone. There has been observed, however, following the feeding of raw liver, an increase of polynuclear eosinophiles much more often and to a much greater degree than when cooked liver or liver extracts have been fed. The increase of these cells usually begins about three weeks after treatment is commenced, and they may constitute even over half of the circulating white blood-cells. After reaching a maximum they decrease slowly, but are apt to remain above normal. The significance of this reaction is not clear and might suggest that the use of raw liver was unwise. Many patients, however, have taken raw liver daily for more than a year, who have had a marked increase of eosinophiles without the development of any untoward symptoms.

Although there is only one essential requirement for successful therapy, namely, that the patient ingest daily an adequate amount of the active principle contained in liver and continue indefinitely to take it with regularity, the patient should, as soon as possible, take a diet, to supply liberally, but not excessively, all the requirements of the body. The diet for each patient should be prescribed individually, taking into account his weight, symptoms, likes, and dislikes. It need not contain any unusual amount of protein, but it seems desirable that the diet contain an abundance of fruits and green vegetables and at least a moderate amount (70 grams) of muscle meat. These foods are desirable ones for any person and can enhance hemoglobin formation (Whipple). Although there has been no important distinction in the improvement of patients treated with whole liver, kidney or liver extract, it appears that the hemoglobin concentration in some instances has risen more slowly in patients treated with extract than in those upon a similar diet except that it contained large amounts of whole liver. The rate of red blood-cell increase does not appear to be influenced, at least within the first two weeks, by the diet that the patient takes. When hemoglobin lags behind the red blood-cell rise in

patients treated with extract, it may be wise to give them some liver to eat in addition to the extract. Patients treated with whole liver have tended to gain more weight than those treated with extract, probably particularly because their diet has contained more calories. Individuals taking whole liver have more often had voracious appetites. This may perhaps be attributed to the large amount of vitamin B in whole liver. It also may be because the ingestion of whole liver, but not the liver extract, decreases the blood-sugar, which can lead to a desire for more food (Murphy and Blotner).

Excess of fat in the diet will not inhibit a rapid growth of the red blood-cells in pernicious anemia, but large amounts may upset the digestion and cause undesirable gain in weight, and theoretically act adversely. Therefore in some cases it may be desirable to restrict fats.

Concentrated carbohydrate foods should not be added in relatively large amounts until the patient is taking other foods well. They have no particularly favorable effect on blood-formation and if sweet or in soggy form, often intensify colonic indigestion. They aid to appease the increasing appetite but it is often desirable to avoid an excess of these foods.

No contra-indication to the use of liver extract is known. Attacks of gout have been observed to develop in patients taking whole liver and perhaps symptoms of chronic arthritis have sometimes been intensified.

There is no evidence that excess of known vitamins in the diet is important for the patient with pernicious anemia. The exact influence of various foodstuffs needs consideration and the studies of Elders, and Koessler and his associates should be extended. Likewise, the rôle played by the regular occurrence of achlorhydria and the disturbed digestive processes, which together with an unbalanced or undesirable diet have often constituted the history of persons with the disease, must also be further studied. Castle's demonstration that the normal gastric contents containing partly digested beefsteak fed patients with pernicious anemia causes a prompt response of the bone-marrow will probably prove of the utmost importance in elucidating the pathologic physiology of the disease. Experiences to date indicate, however, that the anti-pernicious anemia substance is the essential factor in treatment, and the rôle played by other foodstuffs and the disadvantage of achlorhydria in maintaining or improving health must be considered subsidiary.

Treatment with the active principle contained in liver and an adequate well-balanced diet permits the primitive cells that crowd the bone-marrow in relapse to rapidly decrease, so that the marrow assumes a normal histological appearance as the erythrocyte count approaches normal. Coincident with the rising red blood-cell count and concentration of hemoglobin the bile pigments in the plasma soon decrease to normal (Murphy, Monroe, and Fitz). The color index may become less than one. The anisocytosis and macrocytosis of the erythrocytes decrease and in

many cases these cells appear essentially normal when their count is over
4.5 million per cubic millimeter (Medearis and Minot). Increases of
blood-platelets and changes towards normal of the white blood-cells
promptly follow liver therapy.

The patient's symptomatic improvement which occurs with regularity
becomes clearly evident by the time of the peak of the reticulocyte in-
crease and continues in a rapid and startling manner. The individuals
usually appear well, except for the disorders of the central nervous sys-
tem, two months after commencing treatment and by about this time the
blood is almost always essentially normal. Abnormal muscular weakness
without evidence of spinal cord degeneration may persist after the red
blood-cells are present in normal numbers. Gastro-intestinal symptoms
often decrease quickly and tongue symptoms soon vanish. Their recurrence
rarely is to be observed when apparently a suitable amount of liver or
liver extract is taken. Achlorhydria remains present.

A decrease of symptoms referable to the neural system seldom occurs
until the red blood-cells are over 4 million per cubic millimeter, and then
improvement usually develops slowly. Severe damage to this system can-
not be repaired, but improvement of symptoms due to its injury may
continue slowly for more than a year. Numbness often has disappeared
and bone vibration sense has increased. Coördination of the extremities
has improved frequently and occasionally to a high degree. Symptoms
referable to the neural system have rarely—if ever—developed under
adequate therapy. Evidence of progression of central nervous system
lesions after adequate treatment for two months is rare. The active prin-
ciple thus also appears to have a favorable effect on the central nervous
and gastro-intestinal systems, both of which are involved in pernicious
anemia independently of the hemopoietic system.

If central nervous system lesions appear to be progressing, not only
are large amounts of liver, or liver extract, recommended, but also in such
cases perhaps diluted hydrochloric acid (U.S.P.), 5 c.c., well diluted, three
times a day may be helpful. Exercises to retrain and develop muscles
undoubtedly are beneficial for persons with damage to the central nervous
system and should never be neglected.

Although proper treatment permits the health of essentially all patients
with pernicious anemia to improve strikingly and their erythrocytes to
increase to over 4.5 million per cubic millimeter, no matter whether they
have had one or more relapses, occasionally a case will be found to have
progressed so far that death will ensue before there is sufficient time (about
a week) to influence adequately the disease. Improvement will also not be
observed if fatal complications arise before therapy is commenced or
develop during the early days of treatment. However, many very ill
patients, including some in a comatose condition, have become rapidly
better following the administration of 200 or more grams of prepared liver

or kidney, or of standardized extract derived from 500 or 600 grams of liver. It is perhaps wise in desperately ill cases in order to conserve as much time as possible to give standardized liver extract, or its equivalent, derived from as much as from 1,000 to 1,500 grams of liver a day for four days. Rapid progressive improvement continues for more than two weeks after such a massive dose, but it is probably desirable to not omit liver therapy following such an amount, although the daily dose may be greatly reduced.

Experience as recorded above, demonstrates that if at first there is given daily the amount of active principle contained in standardized liver extract derived from 500 or 600 grams of liver, it will permit rapid recovery from a critical condition. Less than this amount may produce an entirely satisfactory improvement in health. After the count is normal the maintenance dose, as described above, must be decided from time to time for each patient. *It is important, however, for the patient to take daily an optimal amount of the active principle. This will be seldom less than the amount contained in standardized extract derived from 300 grams of liver. Furthermore, it must be appreciated that the best results will be obtained when one prescribes large doses that can cause maximal improvement and maintain the best possible health, rather than small doses sufficient to create pronounced improvement and permit a continued fairly satisfactory sense of well-being.* It is emphasized that infections may decrease the red blood-cells rapidly, and if they arise, additional amounts of active principle should be fed.

The patient himself must not be overlooked in the treatment of his disease, but treatment other than the administration in some form of a sufficient amount of the active principle effective in pernicious anemia and an adequate well-balanced diet is subsidiary. Macht's observations on the influence of ultraviolet light suggest that these rays may be a useful adjunct in therapy. Diluted hydrochloric acid (U.S.P.) may aid in improving disordered gastro-intestinal function and have beneficial effects which are not well recognized. Many patients have improved and remained in good health without taking this medicine. If prescribed, large doses (4 to 5 c.c.), well diluted, are advised with each of three meals a day. Transfusion of blood need very seldom be resorted to, although occasionally it may be performed to save suffering and in an emergency. It is unwise to transfuse blood at the time immature cells are flooding the blood stream because thrombosis may perhaps be precipitated. In the usual case transfusion of blood can perhaps do more harm than good if liver therapy is to be carried out.

It is anticipated that the results obtained by liver treatment of pernicious anemia will lead in the near future to more knowledge concerning the disease. It is thus suggested that the current literature be consulted to obtain the latest information concerning pernicious anemia that is

influenced as specifically as vitamin deficiency diseases and some disorders of the internal secretions.

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Papers on the subject presented at the June, 1928, meeting of the American Medical Association by numerous physicians as well as over fifty other papers on the subject have appeared while this article was passing through the press. Many of these articles are synopsized in the Reviews of Literature (May, 1929) of the Nelson Loose-Leaf Medicine. Thomas Nelson & Sons, N. Y.

CHAPTER XXXV

TREATMENT OF ANEMIA, OTHER THAN PERNICIOUS ANEMIA, WITH DIET

George R. Minot

It is probable that many more cases of anemia will be cured in the future by food and its derivatives than by other measures. For a long time diets rich in protein and iron-containing foods, as well as of high caloric value, have been advised for many cases of anemia and they can benefit distinctly some patients. Even so, knowledge concerning the influence on the blood of different sorts of food, or substances they contain, is but in its infancy. Information concerning the character of some of the recent investigations bearing on the problem is briefly presented in the following paragraphs.

Whipple and his associates have demonstrated clearly the important effect of certain foods on the regeneration of hemoglobin in dogs with anemia due to chronic blood-loss. Liver and kidney are most potent, while spleen, pancreas, brain and red muscle meat are about from one-third to one-fourth as effective. Muscle appears to vary widely in its capacity to produce new hemoglobin. Some fruits as apricots, peaches, raisins, apples and prunes are rather more effective in producing hemoglobin than an equal weight of muscle meat, although other fruits are but slightly effective and raspberries are inert. Lettuce, spinach and asparagus have enhanced relatively little the hemoglobin production in Whipple's anemic dogs, but they have done so more than other vegetables, for example, beets and carrots, which in this respect are almost without effect. Milk, fish and most concentrated carbohydrate foods, such as bread, are essentially without influence, while cream, butter and cheese are only very slightly more favorable for hemoglobin regeneration in these dogs. This certainly does not imply, as Whipple emphasizes, that dairy products should not be fed anemic patients for they supply various sorts of nutritious substances. The addition of iron to the diet, at least when there is an actual shortage of this element in the body, can enhance the effect of food on hemoglobin regeneration. Whipple's experiments appear to indicate clearly that the favorable effect of liver feeding in dogs with anemia due to blood-loss is not dependent on the iron alone in the liver parenchyma as believed by some other investigators. Whipple has, however, suggested that inorganic elements may be important factors. He and his associates have very

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recently shown that the inorganic ash of liver, kidney or apricots will produce a notable increase of hemoglobin in their dogs. Synthetic ash compounds have not proved potent. Observations concerning the addition of considerable amounts of simple salts to the dogs' standard ration showed that iron is apparently more potent than copper or zinc in enhancing hemoglobin regeneration. These observations are of interest when contrasted with the reports of Hart and his associates referred to further on.

Scott has shown the value of food containing chlorophyl in the prevention of anemia following repeated small losses of blood in rats. Among other studies, those of McCay on rats and dogs further illustrate the importance of something in food, which may be inorganic, in the regeneration of hemoglobin in experimental anemia. Larsell and associates' recent studies concerning the very positive effect of nuclear extractives of certain cells and organs in experimental anemia and human pernicious anemia are to be noted by students of this subject. Likewise the observations of Leake and Evans concerning the value of extracts of spleen and bone-marrow in the treatment of some cases of "secondary" anemia should be carefully considered and further evaluated.

In anemia produced in babies by a too prolonged diet of milk, often called iron starvation anemia, the administration of iron together with foods rich in iron, such as liver, are remedial. This has been known for about a quarter of a century. When animals (rats in most studies) are placed on a diet composed chiefly of milk, or bread and milk, a progressive "nutritional anemia" develops. Various investigators have reported the beneficial effects of the addition of iron compounds to otherwise unchanged rations. Mitchell, with Schmidt and with Vaughn, have considered that under such circumstances iron contained in molasses and meat, and soluble iron, as ferric acetate, citrate and chlorid, are distinctly more efficacious than less soluble iron as ferrous carbonate, ferric oxid and ferrum reductum. Hart and his associates, however, have demonstrated that highly purified inorganic iron salts fail to influence significantly the hemoglobin level in animals with nutritional anemia. Many foods were found beneficial. These investigators have shown that ashed residues of liver, lettuce and corn, all of which contain small amounts of iron, are effective in curing the anemia produced in rats by a diet of cow's whole milk. The brilliant research of these investigators has led them to demonstrate that the essential element besides iron in curing nutritional anemia is copper and that in this condition copper is vitally concerned in the building of hemoglobin. A trace of copper supplied along with iron salts eliminates nutritional anemia in rats. Copper, Hart considers, thus acts to supplement iron for hemoglobin building in the rat. This discovery must not lead one to suppose that traces of copper with iron will be found a "cure-all" for the many different sorts of anemia in man. Together they have no effect at all in pernicious anemia nor is the ash of liver truly

efficacious as Elden and McCann have shown. They found, however, that the ash had a weak hemopoietic effect, causing a trivial reticulocyte rise and increase of leukocytes, not unlike what I have observed may occur when arsenic is fed patients with pernicious anemia. The observations of Whipple and Hart have been made on different sorts of animals with anemia produced in different ways, which may explain the apparent discrepancies between their reports concerning copper.

The exact influence of the different known vitamins in alleviating anemia in man remains unsolved. Koessler and associates have stressed the importance of a diet rich in vitamins for patients with anemia. When anemia results from a vitamin deficiency, as, for example, in scurvy from an undoubted lack of vitamin C, then, of course, the patient will be cured and anemia vanish by supplying the proper food.

Careful detailed inquiry into the patient's former dietary habits will help to determine the possible influence of diet in many cases of "simple" anemia. A food deficiency of some sort affecting adversely the manufacture of hemoglobin and red blood-cells directly, or indirectly, as, for example, through altered gastro-intestinal function, is often to be seriously considered. An adequate well-balanced diet rich in foods that enhance blood-formation is worthy of prescribing for many patients with anemia, but each case should be looked upon as an individual problem. The addition to the diet of iron, preferably in large amounts, is of distinct advantage in some cases.

Liver feeding is certainly not of value for all types of anemia. Its use and value in "secondary" anemia is a different matter than the therapy of pernicious anemia (Minot, Murphy and Stetson, 1928). At present knowledge regarding the effect of feeding liver or liver extracts in "secondary" anemia is meager. It is emphasized that liver and kidney contain in large amounts other substances useful to the body's economies, such as complete proteins, iron and vitamins, which are not present in purified liver extract which is promptly effective in pernicious anemia, particularly by permitting a rapid manufacture of red blood-corpuscles. Some other substances in liver, which perhaps especially enhance hemoglobin formation, may be the desirable ones for some patients with secondary anemia. Thus, liver extract may be of little value in some cases of anemia where liver is advantageous. Such is probably a true state of affairs as judged from our few observations in the clinic and Robscheit-Robbins' and Whipple's experiments on dogs. They have shown that liver extract No. 343 (N.N.R.) is not nearly as efficacious as equivalent amounts of whole liver in promoting the regeneration of hemoglobin in dogs with anemia due to blood-loss. However, when the combination of a little whole liver with relatively large amounts of the extract is fed, then the dogs' hemoglobin regenerates rapidly.

The beneficial effects of feeding daily about 200 grams of prepared

liver to patients with anemia due to chronic blood-loss does not appear to be as striking as in experimental animals. There are certainly at least some such cases where the red blood-cells will rise rapidly following such therapy and considerably faster than in comparable cases on ordinary diets especially if rich in concentrated carbohydrate food. The increase of the hemoglobin concentration may be entirely satisfactory, yet rise more slowly than the erythrocytes; in other cases it may rise relatively little even when large amounts of liver are taken for weeks. The addition of large amounts of iron (4 grams daily of ferrous carbonate or ferric citrate) to the diet will be found advantageous in many cases of this sort.

Adequate liver therapy in certain cases of anemia other than idiopathic pernicious anemia can produce the same sort of rapid advantageous changes in the blood and thus startling improvement in the patient, as takes place in pernicious anemia. This has occurred in cases with a myeloblastic type of anemia where perhaps the same mechanism may have been operative that produces idiopathic pernicious anemia. For example, in patients with sprue, infestation with *Dibothriocephalus latus,* without removal of the parasite, and in certain cases of cancer of the stomach.

The treatment of sprue with liver or liver extract (Ashford; Minot, Murphy and Stetson; Richardson and Klumpp, and others) may be as strikingly effective as in pernicious anemia, alleviating not only the anemia—sometimes requiring the addition of iron—but also causing the symptoms of the disease to rapidly diminish. The response in sprue is less regular than in pernicious anemia.

Striking and prompt improvement following liver therapy has also been observed to occur in some patients with a "secondary anemia" type of blood-picture. For example, in certain cases of anemia associated with pregnancy and the puerperium, and in atypical cases of severe anemia in some of which an improper diet played an etiological rôle, in some cases of cirrhosis of the liver, and in others where the origin of the anemia has not been evident.

The anemia of infancy and childhood associated with the partaking of an insufficient or improper diet can be favorably influenced by a well-balanced adequate diet, but the feeding of liver to such patients, particularly with optimal amounts of iron, can hasten improvement and permit it to be of a high degree.

Cases of anemia with the blood-picture of "secondary anemia" or chlorosis often due to no well-recognized cause, are relatively common in women and children. Apparently, at least sometimes, the anemia may be dependent upon an improper diet alone or combined with disorders of the gastro-intestinal tract. Usually the anemia is slight but occasionally severe, and infection or chronic blood-loss may intensify the picture. Some such

cases are very chronic, as classically observed in chronic chlorosis with achlorhydria. The daily oral administration of large doses of iron (about 1 gram of iron) will be promptly and distinctly beneficial in many of these sorts of cases. Meulengracht has shown the effectiveness of such treatment in chronic chlorosis. The response of the reticulocytes to iron therapy is being studied and can serve to indicate the value of this metal in a given case and aid to determine if an optimal dose has been taken. Patients responding to iron therapy should be advised to take optimal amounts for many weeks after their blood is normal, because such treatment may prevent relapse.

The milder cases of ill-defined simple anemias, so common in women, frequently may be alleviated by an ordinary proper diet, but the more chronic and severer cases usually are not influenced by such treatment. Liver feeding with optimal iron medication, should be tried in all such cases and the effect of liver extract learned. In many cases extract alone will have no effect, but whole liver may produce some improvement. However, iron therapy appears to be most important and causes, often alone, or when combined with a diet rich in liver, fruit, green vegetables and meat, very rapid improvement to normal in many cases of secondary anemia due to dietary deficiencies or to no well-recognized cause.

Berglund and associates have reported that the feeding of fetal liver, particularly to women with chronic secondary anemia of unknown etiology, can be very beneficial and strikingly enhance hemoglobin synthesis. Results comparable to his have been observed by Minot and Murphy following the feeding of large amounts of iron and calves' liver.

In true aplastic anemia, in anemia due to the different types of leukemia and Hodgkin's disease, and often in anemias associated with infection, as well as in certain other cases of anemia, liver and iron therapy has produced no significant benefit. Slight improvement, and rarely rapid diminution of anemia may occur from feeding liver when lack of blood is attributed to infection. In some cases of secondary anemia associated with cancer, a liver diet may produce considerable and even pronounced regeneration of blood. It is possible that this therapy can have a distinct beneficial effect in some cases of idiopathic chronic thrombopenic purpura.

It is necessary that many patients be studied with properly controlled observations to determine exactly what can be expected from the use of adult and fetal liver and liver extracts, with or without the addition of iron and perhaps copper, before more than tentative statements can be made concerning this sort of treatment in secondary anemias. Apparently, however, even in similar cases liver therapy (200 to 300 grams of prepared liver a day) does not always cause the same response. In one case it may act very favorably and in another insignificantly. The positive effect of treatment with liver in secondary anemia apparently is seldom so

rapid and dramatic as in pernicious anemia and the hemoglobin, when it has increased, often has not returned to normal; but usually when such is the case much greater improvement will occur when optimal amounts of iron are given. At present it may be said that many patients with anemia should be given the benefit of any doubt by the trial for a period of weeks of eating daily large amounts of liver with a proper supply of other foods and iron. The value of liver preparations alone and combined with other therapy is to be evaluated in secondary anemias as often as opportunity presents.

Cases of obscure very chronic anemia in women have been observed who apparently did not respond to about 150 grams of liver a day for over a month, but the patients did improve slowly and greatly upon a well-balanced high caloric diet, rich in cod-liver oil, butter, cream and whole wheat. As mentioned, the foods alleviating scurvy will rapidly lessen the anemia due to this disease and the same apparently occurs in other conditions with anemia due to recognized vitamin deficiency. Liver is rich in vitamins, including the pellagra preventive substance, and thus may alleviate the anemia of diseases due to vitamin lack. Pal considers ergosterol valuable for patients with anemia and ultraviolet light may play a beneficial rôle in some cases. However, one must not lose sight of the fact that large doses of iron can be valuable and that other foods than liver and kidney can lessen certain forms of secondary anemia and that perhaps for particular cases there are some foods that are more valuable than liver.

The problem of feeding is intimately bound up with the care of the digestive system and in each case the proper means should be instituted to promote normal gastro-intestinal function.

Failures in dietotherapy can result from not describing to the patient himself or the dietitian, nurse, cook or person in charge of the case exactly what food is to be served each day. Success often depends on insistence and persuasion that the chosen diet with large enough amounts of liver be taken. Dogmatism is to be avoided and the imagination freely exercised. The patient himself must be cared for and his diet prescribed with infinite pains.

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CHAPTER XXXVI

THE TREATMENT OF THROMBOCYTOPENIC PURPURA HÆMORRHAGICA

Theodore S. Moïse

Introduction.—Werlhoff, in 1740, described a group of cases characterized by spontaneous hemorrhages in the skin, mucous membranes and viscera under the name "morbus maculosis hæmorrhagica." He believed that this condition was a definite disease entity, but subsequent study has shown that it really represents a symptom-complex of unknown etiology. After the discovery of the blood-platelets this group of purpuras was divided into those showing a normal number of blood-platelets and those showing a definite thrombopenia. The descriptive term thrombocytopenic purpura hæmorrhagica is used to designate the particular forms of purpura that are associated with a diminished number of blood-platelets or thrombocytes.

It is certain that purpura may be produced by somewhat different mechanisms and it is likely that the thrombopenic variety itself is not a definite disease entity but only a symptom-complex. In our present state of knowledge the disease can be classified only on the basis of the clinical picture. Thrombocytopenic purpura hæmorrhagica may occur as a primary idiopathic condition or in a symptomatic form secondary to pernicious anemia, lymphatic leukemia, Hodgkin's disease, etc. The idiopathic type has been described as a disease entity under a variety of synonyms, idiopathic purpura hæmorrhagica, Werlhoff's disease, essential thrombopenia, thrombocytopenic purpura hæmorrhagica, etc. This condition may be acute or chronic, continuous or intermittent.

Symptomatology.—The clinical picture of the different forms of the disease are quite similar, varying largely in degree. For convenience, they will be discussed together. This clinical syndrome occurs at any age and in either sex. It is more common in children and young adults. The acute variety may be a rapidly fulminating disease ending fatally. The chronic cases, however, are much more common and vary from the very mild to those closely resembling the acute fulminating form of the disease.

The most important feature is a hemorrhagic tendency manifested by bleeding from mucous membranes with petechiæ and ecchymoses in the skin and mucous membranes. The bleeding varies in degree from a slight oozing to an almost uncontrollable hemorrhage. Epistaxis and bleed-

ing from the gums are the most frequent forms. Bleeding from the gastro-intestinal and genito-urinary tracts also occurs. The purpuric eruption varies greatly in distribution and extent. The rash may appear as numerous very fine petechiæ or as extensive areas of ecchymosis. The skin lesions may occur in successive crops.

Other symptoms and physical signs may be present as a result of the anemia. Fever frequently occurs in acute phases of the disease.

Physical Examination.—The physical examination is essentially negative except for the evidences of hemorrhage mentioned above. The spleen may be enlarged.

Examination of the Blood.—The characteristic blood-findings are a thrombopenia, a prolongation of the bleeding time, an absence of, or a delayed, retraction of the clot and a normal or slightly prolonged coagulation time.

Etiology.—Although the etiology of thrombopenic purpura hæmorrhagica is unknown, a variety of theories have been advanced to explain the pathogenesis of this disease. All of these have been based on attempts to explain the development of the thrombopenia. This feature is a sign, however, and not the cause of the disease. Thrombopenia is not even the sole factor in the occurrence of the hemorrhages as it is well known that certain cases with a low platelet count show no evidence of bleeding. To explain this fact the idea of thrombopenia plus microscopic lesions of the capillaries has been introduced.

Among the more important theories concerning the pathogenesis of purpura hæmorrhagica are: (1) A derangement in platelet formation as a result of an aplastic megakaryocytoxicosis. (2) A thrombolytic activity on the part of the reticulo-endothelial system, particularly in the spleen (Kaznelson). In the absence of splenomegaly the thrombocytolysis may take place in the extralienal reticulo-endothelial system. Kaznelson does not think that the megakaryocytes are insufficient but on the contrary are hyperactive in the attempt to compensate for the normal peripheral loss. (3) A circulating thrombolytic substance which destroys the platelets.

Although there is little doubt that effete platelets are removed from the circulation by the reticulo-endothelial system, it does not necessarily follow that the spleen itself is primarily responsible for the alteration in the platelets in purpura hæmorrhagica. It seems more likely that the spleen is merely carrying out its normal function in removing dead platelets. It is probable that neither hypothesis completely explains the pathologic process. The facts suggests that at least two factors, the thrombopenia and injury to the capillary endothelium, are concerned in the development of the hemorrhages.

Diagnosis.—The diagnosis of thrombocytopenic purpura hæmorrhagica usually presents no difficulties. In chronic forms of purpura it is important to avoid confusion with hemophilia. Except in a quiescent phase of the

chronic intermittent form of the disease the diagnosis is readily made on the basis of the characteristic blood findings enumerated above. It depends on making a thorough blood-examination. A determination of the coagulation time alone, frequently practiced as a routine preoperative procedure to detect a bleeding tendency, is totally inadequate to determine the presence of purpura.

The differential diagnosis between the idiopathic and the symptomatic varieties may be difficult and depends on determining the presence or absence of an associated causative disease.

TREATMENT

The treatment of thrombocytopenic purpura hæmorrhagica is entirely symptomatic in nature, as the etiologic factors causing the condition are unknown. The most characteristic pathologic finding is a reduction in the blood-platelets and accordingly therapeutic efforts have been directed towards increasing the number of thrombocytes and checking the hemorrhages.

It is important in evaluating any therapeutic procedure to recognize that idiopathic purpura hæmorrhagica has, in many instances, a strong tendency to spontaneous remissions and probably complete recovery. In symptomatic purpura the ultimate outcome depends on the associated disease. It is equally important to understand the limitations of and the purposes for which any therapeutic agent is utilized. The advantages of the following important therapeutic procedures will be discussed: (1) transfusion of blood, (2) irradiation with certain forms of radiant energy, and (3) splenectomy.

Blood Transfusion.—The objects of blood transfusion are several: The first is to relieve the anemia. This is most important in the acute fulminating forms of the disease and in very severe chronic cases. In many instances, however, the anemia is only mild and relatively unimportant. The second and more important object is to check the hemorrhages. The third and most important object is to increase the number of circulating platelets. There is no doubt that blood transfusion is a most satisfactory method of accomplishing these ends, although the exact mechanism whereby the platelets increase following transfusion is not clear. In a recent study of this question Engel has shown that the transfused platelets perish very rapidly and that only a very slight rise follows the transfusion of whole blood. It is, therefore, obvious that the value of blood transfusion in purpura does not consist only in a replacement of blood-platelets. The transfusion probably supplies a stimulus to the formation of platelets but it may act merely by tiding the patient over a period of remission until the normal thrombocytopoiesis is resumed.

In the acute types of this disease the use of transfusions must be

early, persistent and vigorous. The intervals between transfusions and the amount of blood given must be determined by the clinical picture in each case. It should be emphasized that many transfusions may be required in severe cases. In chronic forms of the disease a single transfusion will usually produce a prompt cessation of hemorrhage and may have a marked stimulating effect on the formation of platelets. The choice of the method of transfusion lies between the use of (1) unmodified or (2) citrated blood and depends upon the circumstances and experience of the individual. Although the administration of unmodified blood may have certain advantages, the simplicity of the technic of administering citrated blood makes this method preferable in many instances. Gichner has clearly shown that sodium citrate does not inhibit the activity of the platelets *in vitro* and furthermore he was unable to observe that the injection of citrated blood causes a diminution of the recipient's platelets. The accompanying chart gives a graphic record of the increase in the platelets following a single citrate transfusion in a case of chronic thrombocytopenic purpura hæmorrhagica. In this instance the transfusion was followed by almost immediate cessation of all bleeding but its effect on thrombocytogenesis was not evident until the third day (Chart I).

There is no doubt that the transfusion of either citrated or unmodified blood is of great value in the treatment of purpura hæmorrhagica. In acute phases of the disease it is the most important therapeutic agent and may be a life-saving procedure. In chronic forms of thrombopenia beneficial results usually ensue, although they are frequently transient.

Irradiation with Mercury Vapor Quartz Arc.—The use of radiant energy in the treatment of thrombocytopenic purpura hæmorrhagica, as introduced by Sooy and Moïse, is based on the stimulating effect of ultraviolet light on the blood-platelets of laboratory animals and man. In studying the effect of the absence of light on the organism Cramer and Drew observed an abnormally low platelet count in white rats raised in the dark. Exposure of such animals to the mercury vapor quartz lamp was followed by an increase in the number of blood-platelets. Laurens and Sooy reported a stimulating effect of direct sunlight and an inhibitory influence of darkness on the number of erythrocytes and of thrombocytes in white rats. Sooy observed a more marked increase in those constituents of the blood of white rats following exposure to the mercury vapor quartz lamp. Gunn observed a transient increase in the blood-platelets in young rabbits following exposure to a mercury arc. Hardy irradiated young rabbits with a quartz mercury vapor arc and observed that the platelet count was increased following single exposures. The immediate effect with single and successive daily doses was a sharp drop in the thrombocytes, followed by a marked rise above normal. Successive daily exposures caused a progressive increase in the number of platelets.

In experiments with white rats the author has confirmed Hardy's
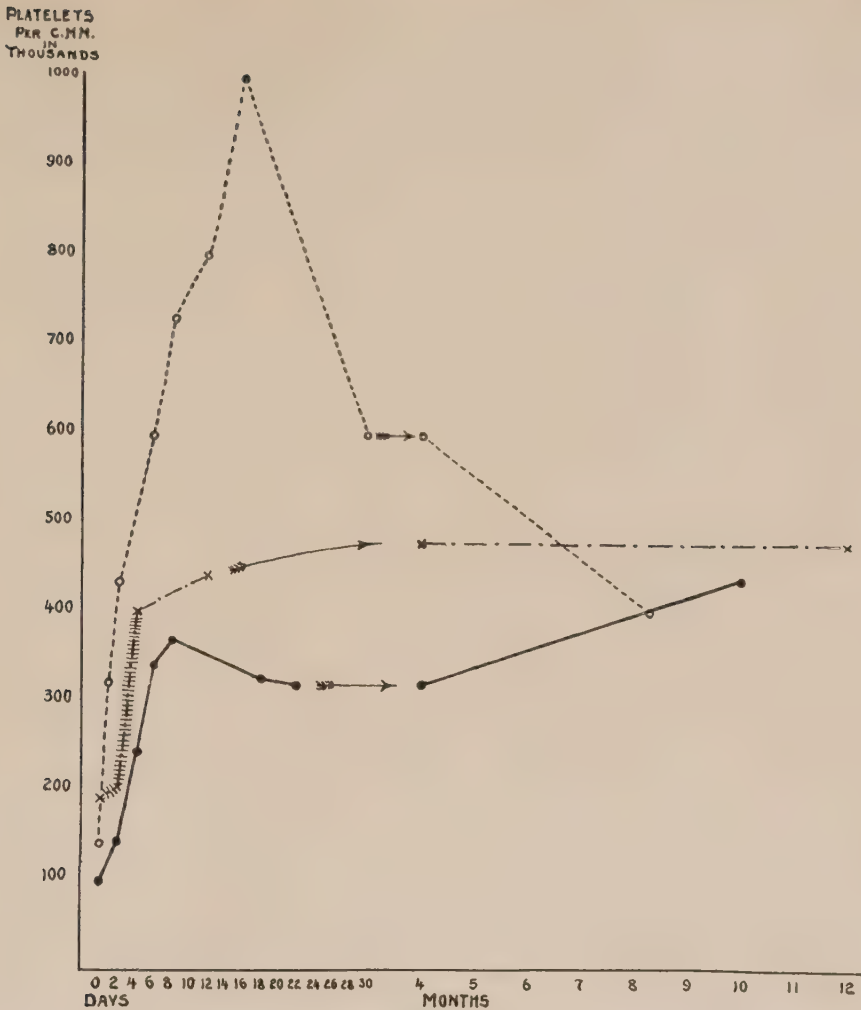
CHART I.—THE CURVES REPRESENT THE EFFECT OF TRANSFUSION, ULTRAVIOLET LIGHT
   AND SPLENECTOMY ON THE BLOOD-PLATELETS IN THROMBOCYTOPENIC PURPURA HÆM-
   ORRHAGICA.
   The solid line shows the rise in platelets observed after a single transfusion of 250
c.c. of citrated blood. The dot and dash line shows the effect of ultraviolet light on the
platelets. The shaded portion of the curve indicates the period during which daily expo-
sures to the mercury vapor quartz arc were given. The broken line shows the changes
in the platelets following splenectomy. The transfusion and the splenectomy were per-
formed at the time indicated by the beginning of the curves. The arrows indicate the
trend of the curves during periods in which no observations were made.

observation concerning the effect of single and of successive daily exposures
to the mercury vapor quartz lamp. The effect of successive daily exposures
has not been entirely consistent as many of the exposed rats showed no
change in the number of thrombocytes. The maximum count appeared
twenty-four hours after a single exposure. In a patient with mild chronic

intermittent purpura hæmorrhagica, thrombocyte counts were made imme-
diately and twenty-four hours after exposure to the mercury vapor quartz
light. The results (Chart II) show a marked drop immediately after,
and a more marked rise twenty-four hours following the exposures, and
confirm Hardy's observations in rabbits. Sanford has observed a transient
increase in the platelets following irradiation of newborn infants with
ultraviolet light.
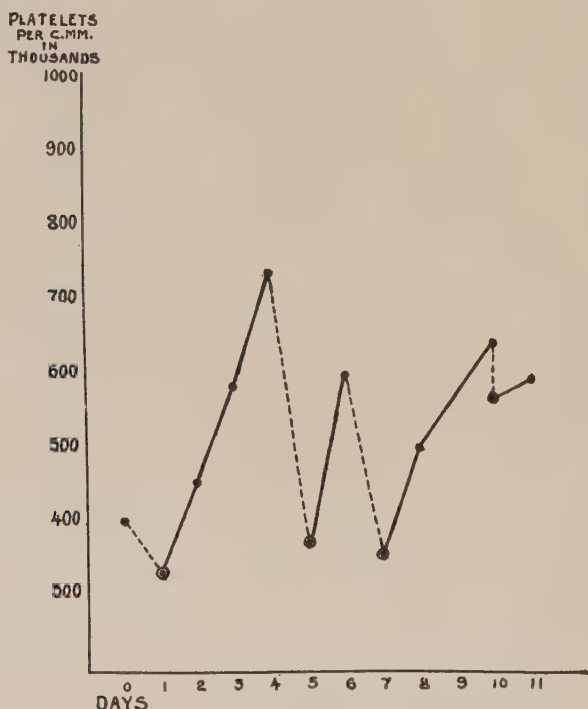
CHART II.—THE CURVE REPRESENTS THE EFFECT OF SUCCESSIVE DAILY IRRADIATIONS
WITH A MERCURY VAPOR QUARTZ ARC ON THE BLOOD-PLATELETS.

The broken lines indicate the drop in the count immediately after irradiation. The
solid lines show the rise in the platelets observed twenty-four hours after successive daily
irradiations.

On the basis of this stimulating effect of ultraviolet light on the
blood-platelets, Sooy and Moïse introduced this form of radiant energy as
an additional therapeutic agent in the treatment of purpura hæmorrhagica.
They observed definite improvement in a group of patients with this con-
dition as judged by clinical observations, and a concomitant return to
normal of the pathologic blood-findings. Tolstoi was unable to observe any
improvement in three cases of chronic thrombocytopenic purpura hæmor-
rhagica treated by this method.

Method of Treatment.—The present method of treatment is as follows:
On the first day the patient is given two exposures of three minutes each,

at a distance of 18 inches, on the entire dorsal and ventral surfaces of the body respectively. The exposures are increased daily by three minutes unless the patient develops a painful erythema. In such cases the painful areas are protected and the exposure is increased in accordance with the individual's tolerance of the light. In no instance has a serious burn been observed.

It is somewhat difficult to be exactly dogmatic about the dosage but the impression has been formed that massive exposures are necessary.

The face and genitalia are protected from the light. It is, of course, particularly important to prevent injury to the eyes.

An air-cooled mercury vapor quartz arc, for use on a 110 D.C. current, has been used as the source of the ultraviolet light.

The effect of the treatment is followed by frequent blood examinations with particular reference to the platelets, the bleeding time and the retractility of the clot.

Results.—The use of radiant energy in the treatment of purpura hæmorrhagica is based on the effect of ultraviolet light on the blood-platelets. Inasmuch as the thrombopenia is certainly not the sole factor in the causation of this disease, it is obvious that a cure should not be expected. It is also obvious that the indication for the use of ultraviolet light is a deficiency in the platelets. The immediate fall in the circulating thrombocytes following irradiation contra-indicates massive exposures in acute fulminating phases of the condition.

In chronic purpura hæmorrhagica beneficial results usually follow this form of treatment. The increase in the blood-platelets is evident within three to five days. The cases fall into three groups: (1) Those in whom improvement occurs promptly and apparently persists; (2) those in whom early improvement is observed but after variable intervals, signs and symptoms, frequently of a minor character, reappear; (3) those cases in whom no benefit is observed. In one such case (Chart II) a splenectomy was followed by definite improvement.

Splenectomy.—The basis for this operation in thrombocytopenic purpura hæmorrhagica, as suggested independently by Hess and Kaznelson, is the splenomegaly observed in this condition and the well-known fact that the blood-platelets increase following splenectomy in normal animals. Kaznelson believed that the enlargement of the spleen indicates that this organ is concerned in the destruction of the blood-platelets in purpura hæmorrhagica. Although the evidence in favor of this theory is presumptive only, definite benefit is being reported, following removal of the spleen in an ever increasing number of patients.

The beneficial effect of splenectomy on thrombopenic purpura suggests that the spleen is in some unknown manner concerned with the mechanism of purpura. In an attempt to elucidate this question Bedson has made an interesting study of the effect of splenectomy on the production of

experimental purpura. He has shown that the purpuric manifestations resulting from the injection of antiplatelet sera are due to two factors: (1) destruction of the platelets and (2) injury to the capillary endothelium. In further studies he has observed that splenectomy (guinea-pigs) is followed by a marked increase in the number of blood-platelets which is apparent within two days, maximal at about two weeks, and returns to normal after three or four weeks.

The injection of an antiplatelet serum in splenectomized guinea-pigs during the period in which the platelets are high shows a relative degree of protection from experimental purpura that is apparently parallel to the increase in the platelet count. By gradually increasing the dosage of antiplatelet serum he was able to destroy a portion or all of the platelets without purpura and all of the platelets with purpura. The injection of antiplatelet serum in splenectomized animals after the thrombocyte count has returned to normal results in purpura with the same dosage as in normal animals. These experiments suggested his conclusion that only temporary relief should be expected in the treatment of purpura hæmorrhagica by splenectomy.

There is a consensus of opinion that an abrupt early rise in the thrombocytes occurs after splenectomy. This is followed by a drop to a normal or low figure within a period varying between a few days and two months after the operation. This is in accord with my own observations (Chart I). It is frequently stated that the bleeding time returns to normal in an immediate and spectacular manner after ligation of the splenic vessels. Although particular note has been made of this point, I have not observed any such miraculous disappearance of the hemorrhagic diathesis. The accompanying observations (Chart I) are quite typical of the changes observed following splenectomy and they clearly illustrate the value of this procedure in chronic thrombocytopenic purpura hæmorrhagica.

In a recent analysis of cases collected from the literature Whipple reports brilliant results following splenectomy in chronic thrombocytopenic purpura hæmorrhagica. In his series, sixty-one patients were followed for periods varying from three months to six and one-half years. Good results were reported in fifty-one instances, fair in four, and poor in six. In thirty-two of these, however, the period of follow-up was less than one year. In certain instances the operation was performed in a quiescent stage of the disease and in others blood transfusion was given a few days before operation. The combination of blood transfusion with other forms of therapy is of course desirable but under such circumstances it is impossible to say just how much each therapeutic agent has contributed to the subsequent improvement. Whipple concludes that splenectomy is contraindicated in the acute fulminating cases on account of the high operative mortality.

SUMMARY

Thrombocytopenic purpura hæmorrhagica is probably not a disease entity but a symptom-complex of unknown etiology. The most important factors in the production of this condition are the thrombopenia and injury to the capillary endothelium. It is unlikely that any of the existing methods of treatment actually bring about a cure, but merely produce an amelioration of the symptoms. This applies to all of the known therapeutic procedures including transfusion of blood, irradiation with ultraviolet light, splenectomy and other methods.

The response of the individuals to the different therapeutic procedures is somewhat variable. One patient will respond to transfusion, another to ultraviolet light or splenectomy and a third to neither. In patients responding favorably to transfusion, radiant energy, or splenectomy, the results may be quite similar at the end of a given period (Chart I). After any of the known methods of treatment recurrence may be observed. The important point to emphasize is that beneficial results have been observed with several different forms of treatment and as removal of the spleen is extremely radical in comparison to the other methods, it should be reserved for those patients who do not respond to treatment by the simpler means.

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CHAPTER XXXVII

DREPANOCYTIC (SICKLE-CELL) ANEMIA

E. Vernon Hahn

Sickle-cell anemia is a clinical entity occurring only in negroes whose red blood-corpuscles are abnormal in that they undergo a striking distortion into crescentic forms under certain conditions. This abnormality of the red blood-corpuscles is apparently hereditary and is transmitted as a unit character, not sex-linked, according to the mendelian law for a dominant trait.

The possession of red blood-corpuscles with the sickle-cell trait does not constitute disease in the ordinary sense of the word. In the family of almost every patient with sickle-cell anemia may be found relatives whose red blood-corpuscles have the characteristic abnormality but who are otherwise perfectly healthy. The sickle-cell trait, therefore, can be regarded as only a constitutional state predisposing to sickle-cell anemia. Sickle-cell anemia, occurring sporadically among individuals with the sickle-cell trait, must be considered the effect of precipitating factors, as yet unknown, which produce anemia only in individuals whose red blood-corpuscles have this peculiar susceptibility.

The name "sickle-cell anemia" has usually been employed loosely to designate both the underlying hereditary abnormality and the anemia to which it predisposes. The inappropriateness of this terminology is apparent and several names have been coined to correct it. The sickle-cell trait has been called "drepanocytemia" and the disease "drepanocytic anemia." Equally good etymologically is the pair of names "meniscocytosis" and "meniscocytic anemia."

CLINICAL PICTURE

Patients with drepanocytic anemia present, according to the severity of the disease, varying degrees of anemia and hemolytic jaundice. They complain of weakness, shortness of breath, palpitation of the heart on exercise, rheumatoid joint pains, and attacks of abdominal pain. Infants and young children manifest lassitude and disinclination for food.

On physical examination one observes emaciation, a greenish tint of the scleræ, pallor of the mucosæ, usually a generalized lymphadenopathy, and occasionally ulcers or the scars of ulcers on the legs. Often the spleen

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and less frequently the liver are enlarged. Splenomegaly, however, is far from being a constant feature even in a given case. The heart is usually enlarged and the murmurs usually associated with severe anemia are present. The upper respiratory tract shows evidence of acute infection in many instances. Râles, impairment of resonance, and Roentgen shadows are frequently sufficient to lead to a provisional diagnosis of broncho-pneumonia.

The disease is characterized by remissions and exacerbations. During exacerbations, the temperature is usually elevated from one to three degrees. Occasionally, there are sharp febrile crises. During remissions, the patients are not entirely well. Their physical endurance is limited and their scleræ remain greenish. It is a striking fact that recurrences of acute illness are usually coincident with attacks of respiratory infection.

The red blood-corpuscles vary in number from well below 1,000,000 to nearly normal. The color index is below 0.7 about as often as above 1.0. The leukocyte count is usually high and may often reach such levels as 20,000 to 30,000. There is nothing abnormal in the differential count.

In smears of the blood stained with Wright's stain, the red corpuscles display marked poikilocytosis and varying degrees of basophilia, both punctate and diffuse. Usually, a few crescentic corpuscles are present but the technic of making stained blood-smears is such that drepanocytes in the circulating blood are not likely to be preserved in their characteristic shape. The reason for this is that exposure to oxygen causes drepanocytes to revert to a circular form, as will be explained later. When stained with brilliant cresyl blue, as high as 40 per cent of the red blood-corpuscles show reticulation. Nucleated red blood-corpuscles may be present in large numbers. Large mononuclear leukocytes with phagocytized red blood-corpuscles have been reported by several observers. There is no significant change in the number of blood-platelets. Bleeding and coagulation times are normal.

When first prepared, an unstained wet smear of the blood under a cover slip, sealed with petrolatum to prevent drying during prolonged observation, shows no peculiarities other than those mentioned in the foregoing, except that occasional crescentic corpuscles are more readily recognized. However, when the smear is examined after the expiration of an hour or so, a large percentage of the red blood-corpuscles are usually found to display the most bizarre distortion into long-horned crescents and filiform shapes, drepanocytes.

The resistance of the red blood-corpuscles in drepanocytic anemia to hypotonic salt solutions is increased. Usually, hemolysis is not apparent in solutions more concentrated than 0.38 per cent and is not complete in solutions more concentrated than 0.20 per cent. Even when hemolysis is apparent at a normal upper level of concentration, it is not complete until an abnormally low level is reached. Thus, the most characteristic

feature of the corpuscles with respect to fragility is a downward extension of the range of concentrations in which hemolysis is only partial.

The blood-plasma shows varying degrees of bilirubinemia. The van den Bergh reaction is negative in the direct phase and positive in the indirect. Quantitatively, serum bilirubin varies from normal values in mild cases to about 15 milligrams per liter. The only other known chemical abnormality of the blood is a moderate increase in cholesterol, in contrast with low values for this substance usually found in other severe anemias. Values averaging 300 milligrams per 100 c.c. have been reported.

The urine and feces contain abnormally large amounts of urobilin. Bilirubin is absent from the urine. Various degrees of albuminuria and cylindruria are common.

INCIDENCE

There is accumulating evidence that the disease is not rare. Approximately one hundred cases have been reported or alluded to in the literature, but owing to the confusion which has existed in terminology, it is not certain how many of these were cases of drepanocytic anemia and how many were merely drepanocytemia. As regards the trait in itself, without reference to the presence or absence of anemia, several studies attempting to ascertain its incidence have been made. By combining the statistics of three clinics, we find that 6.8 per cent of 1,558 negroes had the sickle-cell trait. Examination of the blood of large numbers of white individuals by investigators familiar with the condition has yielded no instance of the sickle-cell trait. In all instances of reports of drepanocytemia in white individuals, there is either grave question as to the purity of the racial stock or the published photomicrographs and descriptions indicate that the abnormality described is not drepanocytemia.

HISTORY

The association of anemia with the occurrence of crescentic red blood-corpuscles was first reported by Herrick, in 1910. Cook and Myer were the first to point out the familial incidence and to claim that the disease constitutes a definite clinical entity. Emmel first reported the gradual transformation of normal appearing red blood-corpuscles into drepanocytes under a sealed cover slip, showing that this phenomenon occurred as readily with the blood of symptomless individuals as with that of anemic subjects. Mason introduced the term "sickle-cell anemia." Sydenstricker, Mulherin and Houseal first reported splenomegaly associated with the anemia and emphasized its hemolytic character. Huck studied the familial incidence of the sickle-cell trait and concluded that it is truly hereditary. He introduced the concept of "latent sickle-cell anemia" (drepanocy-

temia). Sydenstricker summarized his experience with eighty cases, submitting autopsy reports, and concluding that the disease rests on a hereditary defect in the hematopoietic tissues, predisposing the red blood-corpuscles to hemolysis and phagocytosis when unknown activating factors, probably innocuous to normal individuals, accidentally prevail.

Since the earlier reports, the importance of leg ulcers as part of the clinical picture has been less and less emphasized. The most recent publications have concerned themselves chiefly with the therapeutic results of splenectomy and with serological and other details of the sickle-cell distortion *in vitro*.

THE SICKLE-CELL DISTORTION IN VITRO

The red blood-corpuscles of perfectly symptomless individuals with drepanocytemia form drepanocytes as perfectly and as rapidly *in vitro* as do those of patients with the most severe drepanocytic anemia, and the conditions under which the distortion occurs are the same in the two cases.

The phenomenon in sealed wet smears is not constant and of a dozen smears of the blood of a given individual, prepared at the same time and in the same manner, half may show drepanocytes and half may not. For this reason, in attempting diagnosis, drepanocytemia cannot be ruled out unless several slides fail to show the characteristic distortion. Furthermore, in experimental work, the failure of susceptible corpuscles to undergo the distortion under cover slips sealed with petrolatum cannot be accepted as proof that plasma constituents or any other purposely omitted factors are requisite to the distortion.

The drepanocytes in sealed wet smears gradually revert to a circular form after the lapse of a few days. No further distortion occurs in such preparations and the corpuscles gradually undergo lysis. If the cover slip of a sealed wet smear is lifted while the corpuscles are still drepanocytes, the reversion to the circular form is immediate. This phenomenon is consistent with experimental evidence indicating that oxygen causes these peculiar corpuscles to assume a circular shape.

The abnormality which enables red blood-corpuscles to undergo the sickle-cell distortion is apparently inherent in the corpuscles themselves. Many observers have reported that susceptible corpuscles undergo the distortion when suspended in serum from normal individuals and even when suspended in normal saline solution after thorough washing. On the other hand, corpuscles from normal individuals have never been made to undergo the distortion even when mixed with the serum of affected individuals. The few reported experimental results discordant with these statements are probably explained by the technical uncertainty in demonstrating the sickle-cell distortion which has already been pointed out.

The only factors in the immediate environment of susceptible red blood-corpuscles which have conclusively been shown to affect their distortion into drepanocytes are oxygen tension and hydrogen-ion concentration. If a hanging drop of a suspension of susceptible corpuscles in normal saline solution be treated in a gas chamber by a stream of carbon dioxid, hydrogen, nitrous oxid, or ethylene, the corpuscles become drepanocytes. If oxygen is admitted to the chamber, the drepanocytes immediately revert to a circular shape. Carbon monoxid has the same power to restore a circular shape. After restoration of the circular shape, oxygen-free gases again induce the distortion, and a series of reversals may be effected almost indefinitely. The hydrogen-ion concentration must be on the acid side of neutrality before asphyxia suffices to induce the distortion. Inasmuch as an acid reaction favors the dissociation of oxyhemoglobin, it seems safe to assume that the drepanocyte is stable only when the hemoglobin is uncombined and that the circular shape of these peculiar red blood-corpuscles is stable only when the hemoglobin is associated with oxygen (or carbon monoxid).

The fact that drepanocytes formed under a sealed cover slip immediately revert to a circular shape on lifting the cover is consistent with the hypothesis just set forth. Furthermore, the fact that drepanocyte formation in wet smears starts around clumps of leukocytes and spreads peripherally with the lapse of time is explained by the same hypothesis with the additional assumption that the leukocytes live in such smears and carry on a metabolism rendering their environment progressively poorer in oxygen.

PATHOLOGY

In general, the changes observed *postmortem* are those usually associated with a severe hemolytic anemia. There is a marked hyperplasia of the red bone-marrow, implicating both the erythropoietic and leukopoietic elements. The lymph glands are generally hyperplastic. The lymph glands, liver, spleen, and kidneys contain deposits of iron-containing blood-pigment. The liver is usually enlarged. Both the liver and kidneys show various grades of parenchymatous degeneration. Severe pulmonary lesions are frequently noted, varying from bronchopneumonia to extensive tuberculosis. The heart is enlarged and its muscle is abnormally soft. Spleens removed surgically are usually very large and turgid. Their tissue is almost jelly-like and of a dark plum color. Microscopically, the splenic pulp shows a tremendous congestion of the pulp spaces with red blood-corpuscles. The spleens found at autopsy are usually small, wrinkled, and fibrous.

In all of the organs with cells of the "reticulo-endothelial system," erythrophagocytosis is usually to be demonstrated. Even in other organs, an occasional large mononuclear leukocyte with a phagocytized erythrocyte may be found within a vessel lumen.

As might be expected, streptococci and other organisms are frequently isolated by culture of the heart's blood of patients dying of pneumonia or of some other terminal infection. Bacteriemia, however, is not an essential feature of the disease as is shown by occasional negative tissue cultures from patients subjected to splenectomy and negative blood-cultures from patients dying of accidental trauma.

With the exception of one report, all writers who have given consideration to the matter state that sections from tissue blocks fixed in formalin show a marked sickle-cell distortion of the red blood-corpuscles, and that sections from blocks fixed in Zenker's fluid show red blood-corpuscles of apparently normal shape. The same difference in the shape of the fixed corpuscles is to be observed when drepanocytes, formed *in vitro* by passing carbon dioxid through a suspension of susceptible red blood-corpuscles in normal saline solution in a flask, are treated by these two agents. Because of the lability of shape of drepanocytes and because of the uncertainty of the action of standard fixing agents upon them, it is impossible to infer from tissue sections whether or not drepanocytes occur, as such, in the vascular or hemopoietic systems during life.

The presence of drepanocytes in the circulating blood during life is also difficult of demonstration. Ordinary hematological methods suffice for the study of the formed elements which possess considerable stability. The shape of these corpuscles, however, is so sensitive to oxidation-reduction changes of their contained hemoglobin, that the enumeration of drepanocytes in the blood is at the present time impossible. Nevertheless, two facts stand out from which a conclusion can probably be drawn. When wet smears are quickly made with minimum exposure to air and examined promptly before drepanocytes have time to form under the artificial conditions of the blood film, drepanocytes in relatively small numbers are seen in the blood of patients with drepanocytic anemia, and they are not seen in the blood of individuals with drepanocytemia without anemia. Therefore, it seems likely that the distortion of corpuscles into drepanocytes *in vivo* precedes and determines their destruction. This view is supported by the experimental observation that drepanocytes are more susceptible to hemolysis at incubator temperature than normal red blood-cells.

In summary, and as a working hypothesis, the following view of the disease may be presented. Individuals with the sickle-cell trait may lead normal lives without any symptoms of anemia as long as their red blood-corpuscles are not converted into drepanocytes. The unknown noxa which induces the distortion of their corpuscles into drepanocytes may possibly be anoxemia resulting from pulmonary disease, or plasma changes precipitated by exposure to cold, or toxemia resulting from infection. The transformation of normally functioning corpuscles into drepanocytes in the

blood stream subjects them to the action of the usual hemolytic and ery-
throphagic agencies of the body. Anemia and hemolytic jaundice appear
as a consequence, with a severity depending upon the extent of the con-
version of corpuscles into drepanocytes. The spleen, as the most active
hemoclastic organ of the body, accumulates and destroys the damaged
red cells (drepanocytes), gradually undergoing damage in the process.
Later, if the drepanocytic process continues, the lymph-nodes and the liver
take up the hemoclastic activity. During this process, the hematopoietic
tissue of the bone-marrow undergoes compensatory hyperplasia. Thus, for
long periods of time, patients with the disease may remain reasonably com-
fortable and active, adapting themselves to a low level of hemoglobin in
a state of compensated hemolytic anemia.

TREATMENT

The treatment of drepanocytic anemia is not yet established. Hematinic
drugs apparently have no effect. Liver feeding and actinotherapy, if they
have been tried, have not been reported. Blood transfusion is well tol-
erated, but its effect is temporary. Careful dietetic management, as prac-
ticed by pediatricians, has had no favorable effect upon the course of the
disease in infants.

Bed rest and treatment for concomitant respiratory infections are
followed in time by remission. Sooner or later, new respiratory infections
initiate new hemoclastic waves and recurrence of symptoms.

Splenectomy, first suggested by Huck, has been practiced in five cases.
The procedure seems reasonable because of its success in familial hemo-
lytic jaundice which parallels, in general outlines, drepanocytic anemia.
The results have not been altogether consistent, but they are promising.
Removal of the spleen has not affected the tendency of the corpuscles to
undergo the sickle-cell distortion *in vitro*. Furthermore, postoperative
subjects do not show a return to normal red cell counts or hemoglobin
values. But they do show marked symptomatic improvement and decrease
in the degree of bilirubinemia. Removal of the spleen apparently enables
them to regain a state of compensation.

It is noteworthy that the poorer results after splenectomy have been
in those patients in whom the spleens were atrophic. Doubtless, in these
cases, the other depositories of the reticulo-endothelial system had already
taken over the function of hemoclasis. It is probably necessary to differ-
entiate two stages in drepanocytic anemia: namely, the stage of splenic
enlargement when the spleen is the organ destroying the drepanocytes,
and the stage of splenic *atrophy* when the liver and lymph-nodes are
performing that function. Obviously, it is not hopeful to remove an out-
worn, fibrous spleen to correct an excessive hemoclasis which is being
carried on by the lymph-nodes and liver.

It may be asked, if the lymph-nodes and liver take over the hemoclastic function of the spleen after its atrophy from excessive use, why wouldn't these organs do the same thing after splenectomy? The answer is, of course, conjectural. It would appear that before this office can fully be taken over, the improved blood-condition enables the patient to recover from whatever constitutional or local disturbance has led to the excessive production of drepanocytes. In order to justify splenectomy, we must recognize a vicious circle existing between the hemoclastic activity of the spleen and the abnormal state (infection alone, or infection leading to anoxemia) which precipitates the distortion of the susceptible red blood-corpuscles.

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CHAPTER XXXVIII

THE TREATMENT OF POLYCYTHEMIA VERA (ERYTHREMIA)

Herbert Z. Giffin

GENERAL CONSIDERATIONS

The outstanding feature of the altered physiologic process in polycythemia vera is marked increase in the blood volume and in the number of red cells. This necessitates readjustment of the vascular bed and of the physiology of the vascular system. The enlargement of the vascular bed seems to occur first in the larger vessels and vascular organs; it extends, as the disease advances, to the arterioles, capillaries and veins. In the severest cases cyanosis develops in addition to erythrosis. Arteriosclerosis and thrombosis develop and the functions of vital organs finally become impaired. Treatment which reduces blood volume relieves the strain on the vascular system and doubtless preserves function and prolongs life. Other important factors are increased activity of erythrogenic tissue, increased viscosity of the blood, and disturbances in metabolism. Methods of treatment at present are not known which safely and surely decrease erythrogenic activity; therefore, the measures in use are those which decrease blood volume.

VENESECTION

Venesection naturally was suggested first in the treatment of polycythemia vera. A review of the literature on venesection in the treatment of erythremia indicates clearly that temporary symptomatic relief occurs in a majority of the cases from a few days to two or three weeks. In some instances a beneficial effect has not been noted; in others, definite relief has been obtained without a fall in the erythrocyte count. Venesection usually has been done in conjunction with other forms of treatment and it is, therefore, impossible to draw conclusions concerning the ultimate effect of repeated venesection over a long period of time. Hurwitz reported a case in which repeated venesection was used over a period of a year with comparative freedom from subjective symptoms; Richards and Herrmann reported a case in which repeated venesection was used over a period of eight months with satisfactory subjective improvement, and Ritchie, a case in which six consecutive venesections were done with subjective im-

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provement, without, however, causing any change in the number of erythrocytes. Taschenberg's experience seems to indicate that in an apparently resistant case phenylhydrazin was much more effective following venesection than it had been previously.

Reported experience with venesection does not demonstrate that the withdrawal of blood either depresses or stimulates the bone-marrow. It is likely that the subjective improvement is caused merely by temporary reduction in the volume and the viscosity of the blood. There does not seem to be a logical basis for the injection of sodium chlorid solution following venesection; in the cases in which this has been done the effect has not been favorable.

In a series of sixty-four cases of erythremia in my own experience, venesection was used in eighteen, but only in conjunction with other forms of treatment. It has been employed entirely for temporary symptomatic relief with satisfactory results in practically every instance. Loss of blood, chiefly by epistaxis or by excessive and long-continued bleeding after extraction, has occurred in thirteen of the cases and is a natural method of relief. Five patients of the series have been used as donors, one patient six times, another four times, and without any indication that they were unsatisfactory donors or that the polycythemic blood was more effective or less effective than normal blood. These considerations indicate that venesection has a definite rôle in the treatment of erythremia.

RADIOTHERAPY

Notwithstanding the fact that treatment by the Roentgen ray has been given in cases of erythremia since the report of Begg and Bullmore, in 1905, and probably has been employed more frequently than any other form of treatment, it is impossible to arrive at a clear understanding of its value. Treatment in most instances has been carried out either for short periods, or at very irregular intervals, and in conjunction with other lines of treatment without apparent uniformity of method. Rydgaard reported a case in which satisfactory improvement resulted both in the symptoms and in the blood-picture, the patient remaining in satisfactory condition for eighteen months. A similar case was reported by Böttner. Verity reported a case in which the patient was in fairly good condition for three years. On the other hand, cases also have been recorded which have been resistant to treatment by the Roentgen ray. In general the results following such treatment have been fairly satisfactory and the remissions have been of considerable duration. It has been stated that Roentgen rays applied over the spleen alone are of no avail, but experience does not seem to corroborate this statement, although the application of Roentgen rays over spleen and long bones is more effective. I have not been able to find an instance in which definite aplasia of the bone-marrow has been

produced. Temporary reactions usually are not severe. The expense and inconvenience of the treatment, however, frequently are prohibitive.

Roentgen ray treatment in polycythemia vera has been used in thirteen cases under my observation. This experience indicates that the treatment usually is effective, but that in some instances the prolonged use of Roentgen rays, even for three years, at intervals from ten days to a month, failed to keep the patient comfortable. It usually is difficult, either because of the patient's delinquency or inability to obtain proper treatment near home, to have the treatment carried out satisfactorily. In some cases in which considerable Roentgen ray treatment has been given chronic exhaustion has developed of which the patients complain more than of the mechanical effects of polycythemia vera and this exhaustion seems to be more marked than that occurring in the average case of polycythemia vera.

F. A. Ford, in a personal communication, said: "The treatment of erythremia has been with a moderate voltage installation (135 peak kilovolts) applied through two fields covering the shafts of the long bones anteriorly and posteriorly. It is given with a 4 millimeter aluminum filter which permits fairly effective penetration for about 3 to 5 centimeters. The dose is kept relatively low, three-fourths of an erythema dose to each skin surface. Definite measurements have not been made of the dose which actually reaches the bone-marrow; the dose varies considerably with the thickness of the overlying tissues. The same exposure usually is applied in one or two fields over the splenic area. Repetition of treatment depends largely on the blood-count and on the symptoms."

Reports on the use of radium over the spleen have been infrequent. Head recorded a case which was under observation for more than six years, in which radium had been used at intervals with a fairly good result. In five of my cases radium treatment was given for six years with very satisfactory results; in two other cases a favorable temporary effect was obtained.

"The skin surface over the spleen is mapped out into areas about 4 centimeters square. To each of these areas radium is applied, the following equipment being employed: the universal silver tube applicator containing 50 milligrams of radium sulphate (element) filtered through the wall of the applicator (0.5 millimeter silver), 2 millimeters lead, 2 millimeters Para rubber and 2.5 centimeters distance by means of a Balza wood block. The time of application is twelve hours to each area. The application is constant until all areas are exposed." (H. H. Bowing—personal communication).

If radiotherapy, either by means of Roentgen rays or radium, can be carried out conveniently under proper supervision, this method of treatment would seem to be satisfactory, and it is possible that more nearly

permanent inhibition of the production of erythrocytes might be attained than by any other method of treatment.

PHENYLHYDRAZIN

In recent years, the administration of phenylhydrazin hydrochlorid has largely supplanted other methods of treatment. Phenylhydrazin was employed experimentally by Hoppe-Seyler in 1885, and Morawitz and Pratt, in 1908, used it for producing experimental anemia. Its clinical use in erythremia was first recorded by Eppinger and Kloss, in 1918. The first reports in the American literature were by Owen, and among his cases he recorded two cases treated by Dorsey which probably were the first cases in which the treatment was used in this country. Other early reports were made by Taschenberg, Levi, Altnow and Carey, Stealy, and Brown and Giffin. Unnecessarily severe anemia was produced by the initial course of phenylhydrazin in the early cases and the occurrence of peripheral thrombosis was noted; in fact, the treatment by means of phenylhydrazin still must be regarded as in the experimental stage, although the results probably have been more satisfactory than those attained by any other method. Phenylhydrazin has specific effect on the destruction of erythrocytes and an actual hemolytic crisis may be produced by large doses. The blood volume becomes reduced almost entirely as a result of the reduction in cell volume. The symptoms are alleviated and the strain on the vascular system is reduced. An increase in the number of leukocytes occurs during treatment and this effect also may be due to specific stimulation. The platelet count is not appreciably affected. It is still open to question whether the drug has a toxic effect on the liver and kidneys, although definite injury to these organs has not been observed either clinically or experimentally. The blood-urea becomes elevated during treatment, apparently as a result of the rapid destruction of cells rather than as the result of retention, although a certain degree of retention may be caused by an excessive amount of pigment in the tubules of the kidney.

Clinical experience indicates that during treatment, in cases in which the patients have been hospitalized, there is a definitely increased tendency to thrombosis which in advanced cases may be fatal. In the less advanced cases in which treatment is carried out while the patients are ambulatory, the results are consistently satisfactory, especially so far as the symptoms are concerned; vertigo, fullness in the head, neuralgia, mental irritability and pains in the legs disappear, and the patient is able to work regularly. Allen and Giffin gave phenylhydrazin to dogs for 146 days over a period of eight months with a total dosage comparable to that of from four to six years of treatment in man, and the dogs were well at the end of the experiments. Final studies of renal and hepatic function, made one month

after the drug had been discontinued, gave readings that were within normal limits. Thrombosis did not occur in the dogs under observation. Although definite evidence of renal injury could not be obtained it could not be concluded that renal injury had not occurred. Huffman, in a study of metabolism during treatment, demonstrated an increased amount of nitrogen in the urine, in the form of urea, and was not able to exclude the existence of renal injury.

In a series of forty-one cases observed at the Mayo Clinic over a period of four years, very satisfactory results were obtained in twenty-five of these cases following treatment by phenylhydrazin. Symptoms were controlled and the general condition was improved sufficiently to enable the patients to work regularly. In eight advanced cases, with arteriosclerosis and visceral injury, the results were fairly satisfactory. In the four-year period of observation, ten patients died; one patient who had attained very satisfactory results met an accidental death; another died of pneumonia; the remaining deaths occurred in very advanced cases.

Little has been written concerning the untoward effects of treatment of phenylhydrazin. Bryan, in 1927, reported a case of a woman aged sixty-five with advanced arteriosclerosis, loss of weight, and marked enlargement of the liver and spleen, in whom a total dosage of 2.9 grams of phenylhydrazin, administered over a period of seven days, was followed by a rapid reduction in the erythrocyte count to 2,540,000, with resulting coma and death. A similar case occurred in the series at the Mayo Clinic, and it seems to be clearly demonstrated that in an advanced case of polycythemia vera a very small dosage of phenylhydrazin may result in rapid and extreme hemolysis with fatal outcome. Two other patients in the series died with extensive thrombosis, following a small dose of phenylhydrazin; in one of these mesenteric thrombosis had been present; in the other, so far as could be determined, preëxisting extensive thrombosis had not been present.

The experience with phenylhydrazin in the treatment of polycythemia vera indicates that it is the most satisfactory form of treatment in patients aged less than sixty years in whom the condition is not far advanced and who can be treated as ambulatory patients. It should be used very cautiously in advanced cases with arteriosclerosis and visceral changes, in cases in which the patient is bedridden, for patients aged more than sixty years, and for patients who have had extensive preëxisting thrombosis. It seems to be an essential of treatment to keep the circulation free. Passive exercise and massage with the patient in bed do not seem to be sufficient to prevent thrombosis.

In the early cases, 0.1 gram was given two or three times a day until a total of from 4 to 7.5 grams had been administered. This produced severe anemia in most instances from which, however, the patient recovered rapidly. The initial dosage of 0.1 gram twice a day for a total of

from 3 to 4 grams is at present regarded as sufficient. The drug is cumu-lative in its action and hemolysis continues for at least ten days following its discontinuance. The drug should be discontinued, therefore, when the erythrocyte count becomes reduced to 5,000,000 and when sudden and extreme leukocytosis develops. After the initial dose, the patient usually can be maintained in a satisfactory condition with from 0.1 to 0.3 gram a week. The patients have taken the drug themselves on the recurrence of symptoms and in this way have been able to determine the dosage which brings about alleviation of symptoms. Some of the patients have stated that the daily administration of phenylhydrazin does not agree with them as well as the use of an occasional dose.

SPLENECTOMY

Cominotti, in 1900, removed the spleen in a typical case of erythremia. The patient died six weeks after operation and at necropsy caries of the spinal vertebræ was found. Van der Weyde and Van Ijzeren, in 1903, reported splenectomy with death of the patient twenty-five days after operation. At necropsy thrombosis of the portal vein was found. Blad, in 1905, reported splenectomy in a case in which the erythrocytes numbered 11,000,000 in each cubic millimeter; death occurred several hours after operation, and necropsy revealed extensive internal hemorrhage. Schneider, in 1906, was somewhat more successful; seven months later, however, pulmonary tuberculosis developed and the patient died seventeen months after splenectomy. One month following operation the erythrocyte count had become reduced to 4,500,000 in each cubic millimeter; a year after splenectomy the erythrocyte count was reported as normal. Sauer, in 1924, reported splenectomy in a case of erythremia, in which the diagnosis had not been made preceding operation. Following operation, the patient became very cyanotic and the blood so viscous that venesection was done with difficulty. Death occurred twenty days after operation. At the Mayo Clinic, splenectomy has been performed three times in cases of polycy-themia vera. The first patient was operated on in 1921 because of severe, recurrent, gastro-intestinal hemorrhage. Before the operation, the ery-throcyte count had been as high as 9,000,000 in each cubic millimeter, and following hemorrhages extreme anemia had been present. The patient is living and working regularly seven years after splenectomy, and the highest erythrocyte count since then has been 6,440,000 in each cubic millimeter. There has been a gradual rise in the leukocyte count to 150,-000 in each cubic millimeter, but studies of the blood do not show definite evidence of leukemia. The platelet count has been as high as 3,000,000 in each cubic millimeter. The blood volume four years after splenectomy was normal. It has not been necessary to administer phenylhydrazin. An-other patient was operated on in 1927 and one year later was in a satis-

factory condition, with normal blood-count, and has not found it necessary to use phenylhydrazin during the last nine months. The third patient died of intraperitoneal hemorrhage one day following splenectomy. This was an advanced case and the operation was difficult.

Splenectomy can be advised at present in cases of polycythemia vera only on an empiric basis. In cases with severe gastro-intestinal hemorrhage it may be clearly indicated, but it is impossible to see at present any logical reason for advising it otherwise. The fact remains, however, that the physiologic interrelationships between the activities of the spleen and the bone-marrow are not understood. The results in the two cases reported are certainly better than one would have expected.

MISCELLANEOUS METHODS OF TREATMENT

Many drugs have been used in the treatment of erythremia, the mention of which might better be omitted because of inadequate observation or unsatisfactory results. Benzol has been administered with some success. McLester reported five cases, including one of his own, in which benzol had been used; in four of these satisfactory improvement both in the erythrocyte count and in the general condition, occurred. It has been assumed that during the administration of benzol serious leukopenia would be likely to develop; however, in McLester's own case the leukocyte count dropped during treatment from 26,000 to 10,000 in each cubic millimeter but leukopenia was not produced. One of the cases which he reviewed showed a leukocyte count of 5,600 in each cubic millimeter at the beginning of treatment; the count never fell below 4,000 and was later as high as 12,000 in each cubic millimeter. In a second case the count dropped from 10,000 to 5,600 in each cubic millimeter. Although it cannot be stated definitely that leukopenia is not produced during benzol treatment, the reported evidence suggests that it may not be produced. Benzol has often been discontinued because of nausea and gastric distress.

CONCLUSIONS

Venesection, radiotherapy, and the administration of phenylhydrazin are clearly the most effective measures in the treatment of erythremia. Venesection gives temporary relief and the results obtained by radiotherapy are more or less inconclusive because of the difficulty and the expense of its administration. Treatment by means of phenylhydrazin is a satisfactory method of treatment and is especially effective in the less advanced cases. It should be used with caution in patients aged more than sixty with marked arteriosclerosis and visceral changes. Ease of administration is a great advantage in favor of the use of phenylhydrazin; moreover, its effect in reducing cell volume and blood volume brings about im-

provement in the physiology of the circulation and would be expected to postpone the advance of arteriosclerosis. The status of splenectomy is not clear.

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CHAPTER XXXIX

THE TREATMENT OF CIRRHOSIS OF THE LIVER

Leonard G. Rowntree

REVIEW OF PROGRESS

Knowledge of cirrhosis of the liver dates back to antiquity, although the term "cirrhosis," meaning "a tawny color," is modern, a gift from Laennec. Jaundice and ascites were both known to Hippocrates; the etiologic relationship to ascites of constriction of the vascular bed of the liver was appreciated by Galen. Many clinicians of the last century showed a remarkable interest in and knowledge of diseases of the liver; notably, Bright, Frerich and Charcot. Of these, Charcot established the nature, purpose, course and extent of the collateral venous channels so commonly encountered in portal cirrhosis.

Anatomic, Physiologic and Clinical Knowledge.—Considerable that has been learned about the liver during the last two decades affords an improved background to the understanding of its behavior in disease. This is concerned largely with the anatomy, physiology and pathology of the organ and its function in health and disease. In connection with anatomic and pathologic studies of the liver, several contributions are especially worthy of note. These have resulted from the work of McIndoe and Counseller, who have made molds or casts of livers by injecting the vascular and biliary channels with celloidin solutions and subsequently destroying their parenchyma by corrosives. The recognition of the bilateral nature of the vascular and biliary systems of the liver is of great clinical importance in understanding lesions of the liver which are unilateral in nature or which affect half of the organ preponderantly, especially when combined with knowledge of the existence of the selective distribution of portal blood in the liver which has been pointed out recently by Copher and Dick. During the last few years, I have encountered several instances of cirrhosis of the liver, in which the process was confined largely to but half of the organ. The casts of the portal system in cirrhotic livers emphasize the marked constriction of the vascular channels of the liver and the need for extensive collateral channels in portal cirrhosis. McIndoe's perfusion experiments, performed on the portal systems of normal and cirrhotic livers, further demonstrate the striking nature of the constriction of the vascular bed and the extent of collateral circulation. Counseller's

studies of the biliary system indicate that the dilatation of the biliary tree in extrahepatic obstruction of the bile-ducts is much earlier in onset and much greater in degree than hitherto has been recognized. This work affords a more adequate background for the appreciation of the functional injury which must result. The combined studies of all of these investigators reveal the intimate relationship of the biliary and vascular systems of the liver. The intertwining of the portal and biliary systems, which they have demonstrated so well, suggests the possibility of the strangling effect of one system on the other in disease. This may constitute an important factor in the development of mixed types of lesions of the liver.

At present, also, there is a clearer physiologic background for an understanding of the behavior of the liver in disease. The experimental work of Whipple, Mann, and Rous and their collaborators has furnished clearer conceptions of the normal functions of the liver and of the nature of their perversions in disease. Rous has demonstrated the development of hydrohepatosis following biliary obstruction, and the nature of the changes in the bile. Whipple has emphasized the extrahepatic origin of bile pigments, and the hematogenous origin of jaundice, and has denied the existence of an enterohepatic circulation of bilirubin. Mann, Sheard, Bollman and Baldes, by means of spectrophotometric methods, have brought clinching proof of the origin of bilirubin in those organs which are rich in reticulo-endothelial cells, and they have shown, also, the dominant rôle of the bone-marrow in the production of bilirubin. Opie and Alford, Graham and Davis and Whipple have called attention to the protection afforded by carbohydrates when the liver is injured. Mann and Magath have demonstrated the development of hypoglycemia and of a peculiar form of toxemia following extirpation of the liver, and they have emphasized the importance of glucose in combating this toxemia. Greene and Snell, using Aldrich's quantitative modification of the Pettenkofer reaction for bile acids, have shown that bile salts introduced into the circulation disappear rapidly, and are excreted into the bile within two hours. Bile acids stimulate the excretion of bile, but the choleresis is represented largely by increase in water and bile acids, whereas the pigments are relatively unaffected.

These contributions all are exercising a profound influence on current ideas of the physiopathology of hepatic disease. Unfortunately, the clinician has been unable, as yet, to utilize all the fundamental information placed at his disposal by such investigations.

Considerable progress has been made along clinical lines. In recent years, a serious effort has been made to determine the functional capacity of the organ in the presence of disease, and numerous tests of the function of the liver have been suggested and tried. Thus far, significant success is attached only to tests of its excretory function. But these tests of hepatic function are of considerable value in medicine from three standpoints:

Diagnostically, they reveal the presence or absence of disturbed hepatic function, the presence or absence of jaundice, and its nature and degree; prognostically, they afford some evidence concerning the extent of functional impairment but are of less value for predicting the course of the disease; therapeutically, they afford indications for treatment, reveal factors bearing on surgical risk and furnish the basis for individualization in treatment. One familiar with these tests cannot question their practical value in clinical medicine. The tests of most value are those for: (1) serum-bilirubin (van den Bergh) and the bile index; (2) dye retention (phenoltetrachlorphthalein or bromsulphthalein); (3) coagulation time of the blood; (4) fragility of erythrocytes; (5) bile or biliary products in the urine, stools or duodenal contents; and (6) bile acids in the blood. The chief value of the functional tests is the interest they are creating in the more careful clinical study of diseases of the liver.

Classification.—In the matter of classification of the various forms of cirrhosis there is still room for much progress. Cirrhosis constitutes a late phase or even a terminal stage in various forms of hepatic disease; it does not represent a single clinical or pathologic entity. Cirrhosis is chronic in its course and results from prolonged inflammatory, degenerative, or proliferative changes in the liver, brought about by a variety of etiological agents, some of which are already known. Infections, toxins, excessive deposition of pigments, obstruction of the biliary channels, and, possibly, overwork of the liver, one or all may play a part, frequently over a long period of years. Because the liver is a part of the splenohepatic system, and is not an isolated organ, the spleen is involved also in many cases of cirrhosis of the liver. Either organ may be affected primarily or secondarily. Of necessity, this fact tends to complicate the clinical picture and makes difficult the differential diagnosis of the various forms of cirrhosis. Distinctive clinical types of cirrhosis do exist, but a large proportion of them are mixed types and hence they are not satisfactorily differentiated. The history and the etiology afford clues to the nature of the underlying pathologic changes. Osler listed five types of cirrhosis: alcoholic (Laennec), portal, hypertrophic (Hanot), syphilitic, and capsular. Obviously, these groupings include both etiologic and pathologic considerations without regard to a single basis for classification. Hanot's cirrhosis, if a true entity, must be extremely rare. Capsular cirrhosis is quite different and might better be considered in another connection. Those forms of biliary cirrhosis so frequently found complicating chronic obstruction and infection of the biliary tract are not given adequate recognition in most textbooks of medicine.

In my own investigations, I have found difficulty in presenting data with regard to function of the liver in various forms of cirrhosis, because of the inadequacy of our present classification. After many attempts, I now am using the classification as outlined in Table I, in which I have

TABLE I—A CLINICAL CLASSIFICATION OF CIRRHOSIS OF THE LIVER

Portal or ascitic cirrhosis	1. Portal cirrhosis with ascites and small liver (Laennec) 2. Portal cirrhosis with ascites and large liver 3. Portal cirrhosis with ascites and jaundice 4. Large liver without ascites, as portal cirrhosis in pre-ascitic stage	Etiology	1. Primary 2. Secondary to known factors. Toxins: alcohol (Laennec), copper, arsenic, spices, foreign proteins, exophthalmic goiter, eclampsia. Infections: syphilis, malaria, tuberculosis, various parasites Pigment deposits: (hemochromatosis from copper). Biliary obstruction (end-stage). Splenomegaly (Banti's disease)
Biliary or icteric cirrhosis	1. Biliary cirrhosis without extrahepatic obstruction 2. Biliary cirrhosis with extrahepatic obstruction 3. Biliary cirrhosis with ascites (end-stage)	Etiology	1. Primary (Hanot)? 2. Secondary to known agents Toxins Infections: colon bacillus, syphilis Secondary to obstruction (gallstones, tumor, stricture, and so forth)
Mixed cirrhosis	1. Large liver 2. Small liver	Etiology	Secondary to any of the causes listed

made an attempt to present the types, the subvarieties and etiologic factors most frequently encountered. Although still far from perfect, this classification probably will prove somewhat more satisfactory for clinical purposes than most classifications heretofore suggested.

PREVENTION AND TREATMENT OF DISEASE OF THE LIVER IN RELATION TO ETIOLOGIC FACTORS

Rational treatment of disease of the liver demands some knowledge of the etiology, pathology and functional changes underlying and accompanying such disease. In the treatment, as outlined below, an attempt is made to give these factors the consideration to which they are entitled. In the prophylaxis and treatment of cirrhosis, a consideration of the etiologic factors involved is obviously important. Both portal and biliary cirrhosis may result from various toxins and from infections, local or constitutional. An intra-abdominal focus of infection may constitute a more frequent exciting cause of injury to the liver than previously has been believed. The biliary type of cirrhosis is often secondary to obstruction of the biliary channels from gall-stones, tumors, stricture, and so forth. So closely interdependent are the portal and biliary systems that mixed forms of cirrhosis are common and a condition in some respects

resembling portal cirrhosis may result from prolonged biliary obstruction. Infection is frequently superimposed. In some recent investigations (Snell, Greene and Rowntree), with prolonged portal obstruction, ascites or other evidence of cirrhosis of the liver did not develop. On the other hand, dogs subjected to permanent biliary obstruction, and kept alive for three or four months through the use of suitable diets containing much dextrose and water, have developed striking ascites and also marked collateral circulation. Bollman has since shown that a protein diet may greatly accelerate the development of the ascites. Overwork of the liver may constitute an additional factor in the development of hypertrophy and subsequent cirrhosis.

Toxins and Their Control.—In the etiology of disease of the liver, certain toxins play an important rôle. One of the chief offenders, it is generally believed, is alcohol. It is probably fair to say that in the minds of most clinicians, the Laennec type of portal cirrhosis is most frequently due to the abuse of alcohol. This relationship, however, is rejected or questioned by most pathologists, who postulate some associated etiologic factors, copper (Mallory), potassium sulphate, or infection, even when the abuse of alcohol is admitted. Although alcohol is a common cause, it is not the only agent that can cause the Laennec type of cirrhosis. The clinical picture, the gross pathologic picture, even the microscopic picture of Laennec's cirrhosis, may be encountered in cases in which alcohol can be excluded as a cause. Portal cirrhosis of unknown origin is also encountered, and instances of the Laennec type of cirrhosis may occur in non-alcoholic persons with syphilis. The pathologist is sometimes in doubt at necropsy as to whether the cirrhosis is due to alcohol or to syphilis. In spite of a history of syphilis he may be unable to demonstrate any evidence of the presence of syphilitic lesions. In many instances of cirrhosis there is a history both of syphilis and of abuse of alcohol, and in such cases it may prove difficult to determine whether the disease should be ascribed primarily to syphilis or to alcohol.

The present time has afforded an unusual opportunity of ascertaining the relation of alcohol to cirrhosis of the liver (Rowntree, *J. Am. M. Ass.,* 1927). The mortality statistics of the last two decades indicate a relationship between the incidence of chronic alcoholism and of cirrhosis of the liver, and also reveal an effect on the mortality from these two diseases, incident to restrictive legislation concerning alcohol, occasioned by the World War, and as a consequence of prohibition. They indicate that cirrhosis is more common in "wet" than in "dry" states and countries, and in urban than in rural districts. City dwellers consume more alcohol than do inhabitants of the country.

Among other toxic substances which are injurious to the liver, and which may result in the production of cirrhosis, are arsenic, phosphorus, chloroform, phenylhydrazin, trinitrotoluene, tetrachlorethane, trinitro-

phenol and carbon tetrachlorid. Chronic poisoning from copper is impli-
cated in the pathogenesis of hemochromatosis according to Mallory, and
cincophen, in certain cases of acute yellow atrophy which may later result
in cirrhosis. Spices and foreign proteins may also be involved, and the
toxins of exophthalmic goiter and eclampsia may be factors.

There is but little doubt that arsenic which has been used for some
decades in the production of experimental disease of the liver, is still a
potent or potential hepatic irritant even when used in the form of ars-
phenamin and its various derivatives. O'Leary, Snell and Bannick, in a
recent report on two cases of cirrhosis due to arsenic, write:

"The ability of arsenic to produce extensive hepatic injury has long
been recognized, and it has also been recognized that the liver may store
arsenic in chronic poisoning. The exact pathologic changes which lead to
portal obstruction and ascites are not fully understood. Sollman states that
arsenic acts like phosphorus in producing hepatic degeneration of the fatty
type and adds that these changes are more pronounced in poisoning with
inorganic arsenic than with organic preparations. Ullmann makes a simi-
lar statement, noting that the most marked necrotic changes occur about
the central veins. In the Manchester epidemic the livers examined at
necropsy presented the picture of chronic interstitial hepatitis; one of our
cases due to arsenic showed a hobnail type of liver on exploration. One of
Broadbent's cases exhibited a mixed form of intralobular and intracellular
cirrhosis. No doubt the area of fatty degeneration and necrosis are replaced
by connective tissue, eventually producing obstruction of the portal radi-
cles and subsequent ascites."

In arsenical cirrhosis of the liver, marked and lasting improvement
may occur when the arsenic is eliminated and proper treatment insti-
tuted, even after there has been considerable injury to the liver. Appar-
ently the therapeutic indications are fully met by mild saline purgatives,
diuretics, restricted intake of fluids and the avoidance of arsenic, either
as medication or as an occupational hazard. The use of sodium thiosulphate
is also indicated at times. This is given in doses of 0.6 grams in a course
of ten to twelve intravenous injections on alternate days.

Phenylhydrazin warrants special consideration because of its fre-
quent employment in the modern treatment of polycythemia vera. Enlarge-
ment of the liver is frequently observed during this form of treatment.
In every case the liver should be carefully watched throughout the course
of treatment and the drug should be discontinued on the development of
jaundice. To the best of my knowledge, however, a case of cirrhosis from
this cause has not thus far been reported.

In the industries special attention should be directed against the dele-
terious effects of phosphorus, copper, tar, airplane dope, and trinitro-
phenol. I have not been able to incriminate copper in any of my own cases
of cirrhosis or of hemochromatosis.

Infections and Their Management.—Infections of various kinds result in injury to the liver and subsequently in cirrhosis. Hence, their proper management has great significance in relation to cirrhosis. Infections may be of several sorts: general, such as syphilis or typhoid fever, local and focal infections outside the abdominal cavity, intra-abdominal infections, or infections of the liver itself. The infection may be due to pathogenic bacteria or to parasites. The injury to the liver which directly or indirectly results from the reaction of the hepatic parenchyma to infectious processes is of great practical significance. Foci of infection in the appendix and biliary tract are particularly significant. It is recognized that typhoid fever, as well as other infectious diseases, may cause necrotic lesions in the liver. The repair and absorption of such areas conceivably may lead to occlusion of the vascular or biliary tracts and thus may favor the subsequent development of cirrhosis. Typhoid fever also may result in infection of the gall-bladder, with subsequent cholelithiasis, cholangitis and secondary biliary cirrhosis. The prevention of infectious diseases, and their prompt recognition and treatment, thus assume a place of first importance in the prophylaxis of disease of the liver.

This applies also to infestation with certain parasites, notably those of amebiasis, and to malaria. When the etiologic factors persist, specific treatment is indicated. *Amœbea histolytica* is combated by courses of emetin, ipecac and iodo-oxybenzenepyridin-sulphonate (yatren), and malarial hepatitis, by quinin. Certain tropical diseases also demand consideration. Preparations of antimony are the best treatment for kala azar, Egyptian splenomegaly and Katayama disease. A satisfactory treatment is not known for clonorchiasis which sometimes gives rise to biliary cirrhosis with jaundice. Weil's disease probably represents a specific infection and specific serum may prove helpful.

Chief among the constitutional infections resulting in disease of the liver is syphilis. Various pathologic lesions are found in syphilis of the liver; some of these relate to the infection itself; others, in part at least, to the treatment employed. Among the acute lesions are diffuse syphilitic hepatitis in the early stages of syphilis. In some instances, the clinical picture is that of chronic biliary cirrhosis; in others, the nodular surface of hepar lobatum is recognized and portal cirrhosis is encountered, with either a large or a small liver. Alcoholism is sometimes present and is perhaps simultaneously responsible. Occasionally, cases clinically considered syphilis of the liver and treated as such, reveal, at necropsy, portal cirrhosis; the liver is indistinguishable grossly and by ordinary pathologic technic from that of Laennec's type of cirrhosis.

The serologic evidence is important in the diagnosis of syphilis of the liver; in 90 per cent of cases in my series and 80 per cent of the cases discussed by McRae, the Wassermann test of the blood was positive. The history and local manifestations and the constitutional evidence of syphilis

are extremely important, as is also information relating to former treatment with arsphenamin.

The treatment of hepatic syphilis, as advocated in the Mayo Clinic, has for its fundamental principle the cautious administration of mercury and iodids, in order that the replacement fibrosis will take place slowly and that sufficient time will be allowed for the collateral circulation to develop. O'Leary has stated emphatically that the administration of any of the preparations of arsenic in the early treatment of syphilitic disease of the liver is frequently attended with more harm than good; an intractable cirrhosis may develop rapidly in a liver that is affected by diffuse syphilitic hepatitis, or in a gummatous liver following the use of arsphenamin. I recommend the continuance of mercury and potassium by mouth, until the possibility of a Herxheimer reaction is eliminated and the patient begins to show definite clinical signs of improvement. This may require several months. At the end of this time, the administration of mercury by inunction or by injection may be started. This conservative oral method of administration permits one to observe the effect of mercury on the kidney, the importance of which is manifest since a moderate or mild degree of renal injury is usually associated with syphilitic disease of the liver. Occasionally, if other manifestations of syphilis require more intensive treatment, arsphenamin may be used, but only after cautious preliminary treatment with iodids and mercury. In the small group of patients (from 10 to 20 per cent) in which the diagnosis of hepatic syphilis is doubtful, and serologic data are negative, provocative measures and the therapeutic test must often be relied on. This may be carried out along the lines just described, and the use of arsphenamin is best avoided except in rare instances.

It is possible that once the liver has been injured, any infection, even a severe cold, may constitute a cause for acute exacerbation. This is not generally recognized, although it is accepted in relation to exacerbations in chronic nephritis.

The Rôle of Obstruction of the Biliary Tract.—Extrahepatic obstruction of the bile-ducts may lead to cholangitis, hepatitis, and, if constant or intermittent over long periods of time, may lead from intrahepatic or extrahepatic disease to cirrhosis, particularly the biliary type. Obstruction of the bile passages may be the result of changes in the walls of the bile-ducts, caused by neoplasm, or stricture; or the obstruction may be from without, as the result of inflammatory masses, especially tumor of the head of the pancreas. In obstructive jaundice, medical treatment is of little avail, and surgical measures are instituted, depending upon the degree of obstruction and the degree of cirrhosis. In the presence of cirrhosis following obstruction of the bile-ducts, each case must be treated individually.

Certain dietary and hygienic measures may be tried in diseases of the bile passages, but they are not of sufficient efficacy to warrant postponing

operation in severe cases. The most acceptable diet for patients with cholecystic disease is one in which fatty foods are restricted, particularly those rich in cholesterol. The total intake of food is reduced in the obese, and a bland diet is given when reflex gastric disturbances are marked. Hydrochloric acid is used for anacidity and subacidity.

Cholagogues do not play an important rôle in the present treatment of disease of the liver. Bile and bile acids are the only preparations which have a true stimulating effect on the secretion of bile. Greene and Snell have recently shown that they effect an increase in volume rather than changes in the concentration of bile. For emptying the gall-bladder, magnesium sulphate, egg-yolk and oleic acid are employed, but without great success.

Antiseptics for the biliary tract have been sought for many years. Much was expected originally of methenamin, but it has proved unsatisfactory. Mercurochrome − 220 soluble has also been tried, but experimental studies hold out little in the way of prospects and the clinical trials have been disappointing.

It is probable, in certain diseases involving marked destruction of blood, that the liver is subjected to overwork and that hence it hypertrophies. This persists for variable periods and is followed by atrophy and cirrhosis. Such a sequence of events may be occurring in the course of hemolytic icterus. The removal of the spleen in such cases is a great protection to the liver. Splenectomy as a rule is followed by return of the erythrocytes to a normal state of fragility and by the disappearance of jaundice. The course of events in hemolytic jaundice is probably different from that in splenic anemia.

PROPHYLAXIS AND TREATMENT IN RELATION TO THE UNDER- LYING PATHOLOGIC FACTORS

In the general management of cirrhosis, treatment is directed toward the most outstanding anatomic disturbance: in ascitic cirrhosis, primarily toward the alleviation of the results of portal obstruction, and in icteric cirrhosis, to the relief of biliary obstruction or biliary infection. In some instances both biliary and portal obstruction demand consideration.

Portal Cirrhosis.—Usually the patient with portal cirrhosis seeks medical aid for one of two reasons: swelling of the abdomen (ascites) or hemorrhage from esophageal varices and the resulting anemia. Therefore, the management of these conditions constitutes the most important therapeutic consideration.

1. *The Management of Ascites.*—As a rule ascites develops late in cirrhosis. Tapping, or abdominal paracentesis, is practiced to-day as it was practiced in ancient times. It is mentioned in the days of Hippocrates and Galen and is described in detail by Celsus and Paulus Ægineta. Its prac-

tice was condemned by Asclepiades and by Soranus. If employed at all, it is best done early, according to most authorities, and it should be repeated as indicated by clinical necessity. White has emphasized that repeated tappings infrequently are necessary in alcoholic cirrhosis, the patient often succumbing before reaccumulation is possible. This has not been my experience. When tapping has failed, some form of omentopexy usually is resorted to; most often the so-called Talma-Morison operation is employed.

During the last few years, true progress has been made in the medical management of cirrhosis of the liver through the employment of the newer diuretics (Rowntree, Kuth and Barrier). Merbaphen (novasurol, salyrgan) has been found effective in the control of ascites accompanying cirrhosis of the liver. It exerts a marked and most beneficial diuretic effect. In the process, fluid is absorbed from the abdomen in large quantities and is passed on into the urine, frequently in quantities of 3 to 5 liters a day. Patients with ascites of hepatic origin often lose as much as 2 to 3 kilograms and occasionally as much as 5 kilograms in twenty-four hours, following a single intravenous injection of the drug. The intravenous injection of merbaphen may be repeated in most instances at intervals of four to ten days, and in most instances each dose of the drug results in the loss of 2 to 3 kilograms of ascitic fluid. By such means, in the majority of early cases of cirrhosis, the ascites can be entirely removed and in some instances reaccumulation is prevented. Even in old and advanced cases of cirrhosis, and sometimes after repeated tappings, this treatment is successful, though its best effects, as a rule, are evidenced in the earlier stages of the disease.

Merbaphen is a double salt of sodium mercurichlorphenyl-oxyacetate with diethyl barbituric acid (barbital) and contains 33.9 per cent of mercury. It was introduced originally by Zieler as a treatment for syphilis, but through the work of Saxl and Heilig it is being employed at present in various diseases complicated by edema. Since the beginning of the nineteenth century, compounds of mercury have been recommended as diuretics by certain authors, but they have failed of general success because of ineffectiveness or of untoward or toxic effects. Merbaphen has a definite advantage over metallic mercury and mild mercurous chlorid (calomel) in that it is freely soluble in water and may be administered by subcutaneous, intramuscular or intravenous injections.

Untoward effects are not infrequent and hence the drug must be used with great care and the patient must be under almost continuous observation during the period of treatment. In order to determine whether or not the patient is hypersensitive to the drug, 0.5 c.c. is given subcutaneously and the patient is observed over a period of twenty-four hours. In the event of untoward local, constitutional or visceral reaction, great care is subsequently exercised in its use. Mild, unfavorable reactions do not con-

stitute a rigid contra-indication. I have observed untoward reactions, such as diarrhea and even blood-stained stools and purpura; but I have continued to use the drug and have used it successfully, without harm, in cases which have exhibited definite untoward effects after one injection. Just what causes the reaction to appear at one time and not at another is difficult to understand.

The most frequent untoward effect from merbaphen is diarrhea, occasionally associated with cramps and with bloody diarrhea. This may prove
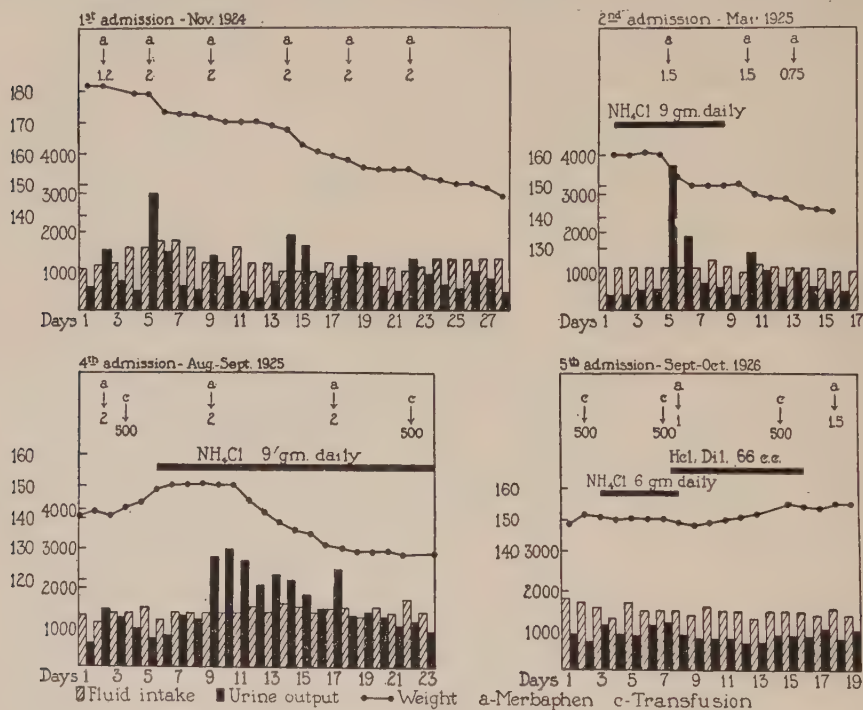
FIG. 1.—TREATMENT OF ASCITES IN PORTAL CIRRHOSIS.

alarming to the patient, the family and the nurse, though it has never, in my experience, proved fatal. It is controlled spontaneously, as a rule lasting but one to two days. If severe or prolonged, it usually yields readily to bismuth or opiates. Sometimes purpuric spots are observed and these are most frequently seen on the arm as the result of application of the cuff of the blood-pressure apparatus. Occasionally the purpura is more widespread and marked. Disturbed permeability and decreased capillary resistance is apparent on applying the tourniquet test. In one or two instances, more widespread dermatitis medicamentosa has been noted. This may be accompanied at times by tenderness of the teeth on snapping the jaws together, or by actual gingivitis and salivation, if the drug is pushed unduly. Albuminuria, and other evidence of renal irritation, such

as erythrocytes and casts, may appear in the urine if due care is not paid to the size of the dose and the frequency of administration. However, experience has taught me that much good can be accomplished with little if any injury provided proper judgment is exercised in the use of merbaphen.

Restriction of the intake of fluid is of paramount importance in the prevention and cure of ascites. In this connection, I believe the advice of older writers in regard to drinking large quantities of water with the idea of stimulating elimination in the early and hypertrophic stages of cirrhosis, is open to question. Proof is lacking that excessive ingestion of water increases elimination or is beneficial in any other respect. Certainly, as soon as ascites develops, restriction of water is a consideration of primary importance. During the treatment of ascites, when possible the intake of water should not exceed 800 c.c. a day. Restriction of salt is also desirable. In this connection a diet low in both water and salt has been developed by my colleague, Keith, which proves helpful, especially in cases that are resistant to treatment. The diet contains 800 c.c. of water, and inorganic ions as follows: sodium, 0.49 gram; potassium, 1.76 gram; calcium, 0.23 gram; magnesium, 0.20 gram, and chlorin, 0.74 gram. An additional 800 c.c. of water is allowed. Although this rigid restriction may not always be necessary, the importance of a diet low in fluids and basic ions, particularly sodium, cannot be overemphasized. The diets may be varied in protein and caloric value with little increase in the content of mineral or water. A sample diet list is shown in Table II.

Other diuretics may be used to enhance the value of merbaphen. In combating edema and ascites, Blum suggested calcium salts. Keith has used ammonium salts with great success, especially the chlorid and nitrate; he has given them orally, in capsules, up to 6 to 10 grams a day. This amount is usually well tolerated for considerable periods without undue gastro-intestinal irritations. Keith has demonstrated that the diuresis of merbaphen is more marked in the presence of a high level of chlorids in the blood. In this connection, I have had good results from large amounts of dilute hydrochloric acid, 20 to 50 c.c., administered by mouth in divided doses in specially prepared capsules. This may be used to replace the ammonium salts, particularly when the blood-urea is increased.

Although the ammonium salts are of unquestionable value, they cannot be employed heedlessly. Acidosis may result, and hence it is necessary to follow the carbon dioxid combining power of the serum. Also, urea may accumulate in the blood and hence its level in the serum must also be checked at intervals of days. Gastro-intestinal irritation, nausea and vomiting may result, and, if severe, may necessitate withdrawal of the drug. In one or two instances, mild psychic disturbances have been encountered during the use of ammonium salts. Cyanosis, of rather sudden onset and unassociated with dyspnea, has been observed in two or three instances during the use of ammonium nitrate. This was associated with methemo-

TABLE II—WEIGHED LOW SALT, LOW FLUID DIET

Breakfast	Grams
10 per cent fruit	100
Egg (one)	
Toast	20
Butter	10
Sugar	5
Dinner	
5 per cent vegetable......................	100
Rice	100
Banana	100
Meat	45
Mayonnaise	15
Bread	20
Butter	15
Sugar	5
Supper	
5 per cent vegetable......................	100
Macaroni	100
15 per cent fruit.........................	100
10 per cent fruit	100
Bread	20
Butter	15
Egg (one)	
Mayonnaise	15
Sugar	5

globinemia. The cyanosis cleared up in each instance within twenty-four to forty-eight hours after the ammonium nitrate had been discontinued.

In summary, the regimen that now is employed in portal cirrhosis with ascites, is effective in perhaps 75 per cent of the cases. The patient is given 0.5 c.c. of merbaphen on admission and is placed on a low intake of fluid and a low salt diet; he also is given ammonium chlorid or ammonium nitrate in amounts of 5 to 10 grams a day. In case contra-indications do not exist, he is given 4 to 6 doses of merbaphen at intervals of four to six days, or until the ascites is controlled. Untoward results following any injection necessitate careful consideration for its further use. The carbon dioxid carrying capacity of the blood, blood-urea and blood chlorids are determined at weekly intervals, or oftener if necessary. Intolerance to the drug or resistance to its influence call for paracentesis, after which the same measures as before may be employed, but they may be applied in milder form to prevent reaccumulation of the ascitic fluid. Other diuretics, such as the purin derivatives, especially euphyllin, are of help occasionally. On rare occasions, resort is made to purgation.

When these measures fail permanently, abdominal paracentesis or operation must be considered. Tapping is employed in all urgent cases, and when the medical regimen has been tried without complete success.

Evidences of toxemia and of a high level of blood-urea make tapping the method of choice. Surgical procedures are justified, if patients are in relatively good condition, but continue to develop ascites despite medical treatment and tapping. Patients with marked cirrhosis are not, as a rule, good surgical risks. Some form of Talma-Morison operation is often indicated. A method of omentopexy of the Talma-Morison type, developed by W. J. Mayo, has yielded good results in a considerable number of cases. It consists of placing the omentum in a pocket especially prepared for it under the right rectus muscle. Splenectomy has also been helpful in some instances when splenomegaly is present, but these cases of cirrhosis are probably of splenic origin and present the Banti syndrome. Whenever operative interference is considered necessary, tests of hepatic function should be made. A high grade of retention of dye in cirrhosis of the liver is indicative of serious risk. With retention of dye, graded 2 to 4, splenectomy is fraught with extreme danger; the patient runs grave risk of the development of insufficiency of the liver. Prior to operation, in portal cirrhosis, diuretics or paracentesis frequently are employed.

2. *The Management of Hemorrhage and Anemia.*—Hemorrhage in portal cirrhosis occurs almost uniformly from varices in one small area in the lower 5 to 10 centimeters of the esophagus. The bleeding may be profuse and intermittent, but it is sometimes more in the nature of prolonged oozing. As time goes on it tends to become more frequent and anemia becomes extreme. At this stage, repeated transfusions are indicated. With the success now attending the management of ascites, hemorrhage and the resulting anemia are assuming increased importance. Thus, in a series of twenty-six cases, satisfactorily controlled from the standpoint of ascites, thirteen patients died within a period of two to four years, of hemorrhage and secondary anemia.

The course of events is adequately portrayed in Figure 1 which shows the condition of the same patient on four different admissions. In the first period of hospitalization, the ascites was adequately controlled by merbaphen; in the second, ammonium salts were employed and two transfusions were given; in the third, treatment with repeated transfusion was directed especially to the anemia, and in the fourth and fifth periods, ascites was not marked, but was more difficult to control than in the earlier stages, and anemia was marked and progressive. This patient's life was probably prolonged for three years beyond the natural course, and he died of anemia and inanition. In this connection, I am now employing liver extract. Iron and arsenic are also usually employed, probably without much basis or much effect. Arsenic may prove dangerous, as already indicated.

This question of hemorrhage from the esophagus is a purely mechanical one, and demands surgical consideration. The esophageal

varices are fed by blood coming up from the left coronary branch of the portal vein, and some method should be sought whereby the blood supply to these veins could be interrupted. Section and ligation of this vein should cut off the main source of blood supply to the esophageal varices and hence control hemorrhage. This procedure has been carried out at my suggestion in two cases by Walters and McIndoe with results that, to date, are excellent.

Biliary Cirrhosis.—This form of cirrhosis is characterized clinically, as a rule, by a large liver and by disturbance of the biliary function, and usually is accompanied by jaundice. It may be primary or it may come as the result of various etiologic factors. The most common forms of it are those associated with obstruction, cholecystitis, cholelithiasis, cholangitis, hepatitis and secondary infections. Toxic or infectious hepatitis occurs at times without obstruction and is accompanied by jaundice of intrahepatic origin. The treatment is symptomatic and should be directed toward the underlying cause when possible. Careful dieting and gastric sedatives may prove helpful. Jaundice, with its attending pruritus, gastric irritation and disturbed coagulation of blood, frequently demands therapeutic consideration. Duodenal drainage is of help in some instances. In all cases in which there is obstruction, surgery offers the most satisfactory treatment. The nature of the procedure is usually determined at operation.

1. *Jaundice.*—This is usually referred to as a symptom, but in reality it represents a retention, or at least an excess, of bile in the blood and tissues. It is attended clinically by icterus, sometimes by pruritis, changes in coagulation of the blood, changes in capillary permeability, hemorrhage, purpura, gastro-enterologic disturbances, anorexia, loss of weight, fatty stools, and other signs.

The treatment depends on the cause. When the jaundice is due to obstruction which is complete and permanent, surgical measures must be resorted to. When the obstruction is intermittent, surgical treatment depends on the extent and degree of the obstruction. In hemolytic jaundice, the removal of the spleen is the treatment usually advised and it is very effective. In intrahepatic types of jaundice, duodenal drainage and dietary and symptomatic measures of relief are employed.

2. *Pruritus.*—This symptom may be slight and easily controlled, or it may be so severe as to dominate the whole clinical picture. Nothing is more terrible to a patient than severe continuous itching which torments him day and night. The cause of itching in disease of the liver is not entirely clear. That it is commonly associated with jaundice is known to every physician. It may occur, however, in portal cirrhosis and in carcinoma of the liver, when jaundice is slight or even lacking. Certain French writers have ascribed it to the excess of bile salts. A study of this question, using the quantitative Pettenkofer reaction of Aldrich in esti-

mating bile salts in the blood, would seem to exclude a direct casual relationship between the bile salts and the pruritus.

Pruritus is best controlled in most cases by mild mercurous chlorid, a fact well known to many general practitioners, but one that is frequently overlooked in hospitals, in clinics and in textbooks. Eppinger has recently reported on its value. In my experience it has great value in a considerable proportion of cases, acting almost in the nature of a specific. The drug is given in amounts up to 2 grains (0.06 to 0.13 gram) in divided doses of 0.25 to 0.5 grain (16 to 32 milligrams) at half-hour intervals, and it may be repeated at intervals of three to six days as needed. The dose and frequency naturally must be suited to the individual case, and evidence of mercurial poisoning should be watched for constantly.

Diathermy is of great value at times; but in other instances, for some unknown reason, it fails utterly. Sweating occasionally relieves pruritus, but, on the other hand, may precipitate it. Daily duodenal drainage may also prove helpful. Antipruritic lotions, such as calamine or colloid baths, may also help at times. When these measures fail, sedatives are often indicated in order to secure sleep. Control of obstructive jaundice usually brings prompt relief of the pruritus.

3. *Hemorrhage and Anemia.*—Severe and sudden hemorrhages from esophageal varices have been discussed in earlier paragraphs. Epistaxis, or oozing from the mucous membranes, and purpura are frequently associated with jaundice. It is most common in the presence of profound jaundice. The loss of blood is rarely rapid. It is usually in the nature of the oozing which continues over many hours. Attempts at local control, particularly in the nose and throat, are as a rule ineffective. Application of epinephrin and iron, alone or in combination, together with packing of the nasal cavities, may be tried. Even these, however, frequently prove of no avail.

Preoperative and Postoperative Treatment of Cirrhosis of the Liver.—In cirrhosis in the presence of jaundice, the preoperative measures advocated by Walters serve materially to reduce the mortality and the incidence of hemorrhage subsequent to operation. This treatment consists in the following: Repeated estimation of the coagulation time of the blood; the administration of calcium chlorid, 5 c.c. of a 10 per cent solution on three successive days; the administration of large quantities of water, and an abundance of carbohydrate foods. Candy is employed frequently. When the coagulation time indicates that the patients are failing to respond to these measures, transfusions usually are employed. McVicar considers transfusions of the greatest value in the prevention of bleeding.

In postoperative treatment, as a rule nothing more than careful observation is necessary. When bile is draining, the quantity should be known. Two types of toxemia have been recognized: In one there is decreased flow of bile with increased level of urea and bilirubin in the blood; in the

second type there is a greatly increased flow of very dilute bile, which is followed by dehydration, exhaustion and collapse. The treatment of postoperative complications should be individualized. Water is probably the most important single factor. It is usually given, as already indicated, as 10 per cent glucose, or as 10 per cent glucose in physiologic solution of sodium chlorid. Whether alkali, salt or glucose should be administered depends on the results of clinical laboratory determinations.

COMPLICATIONS

Congestion.—Congestion of the liver is frequently associated with cardiac decompensation, often as an early manifestation; but with long-continued, chronic passive congestion, a form of hepatic fibrosis or cirrhosis often develops which is associated with ascites. The treatment is essentially that of the underlying cardiac decompensation: Digitalis and restriction of the intake of fluids and of salt. In some instances, diuretics prove helpful and may be given in the form of caffein, theobromin, theocin, and euphyllin. In such conditions, Addison's pill, a combination of squill and digitalis, has been used for nearly a century. Merbaphen and ammonium salts may be used as outlined. In view of the recent introduction of merbaphen, it is interesting that Jendrassik, in 1891, reported favorably on the use of mild mercurous chlorid as a diuretic in this condition. Cathartics, such as Epsom salts, in concentrated form, used after the method of Hay, also prove helpful adjuvants.

Toxemia Accompanying Insufficiency of the Liver.—Various forms of toxemia are encountered in hepatic disease. Some of these appear to be due to hepatic insufficiency. The most common types are those seen in the terminal stages of cirrhosis of the liver and are characterized by a form of coma and narcosis which closely resembles normal sleep. The narcotized patient with portal cirrhosis is as a rule little affected by treatment. In many instances, the intravenous administration of large quantities (800 to 1200 c.c.) of 10 per cent solution of glucose results within two or three hours after the injection in the temporary reëstablishment of consciousness. During this period, consciousness may be restored to the extent that the patient may recognize his friends. In most cases, however, it is of short duration, and the patient lapses again into a coma which ends in death. Occasionally, but not often, this coma clears up; but this is usually spontaneous and is not due to treatment. The second form of toxemia is associated with convulsions or tremor and spasm of the extremities, and it is treated by the intravenous administration of glucose. Another form is associated with infection and febrile reaction. This condition calls for rest, restriction of food, careful nursing, large quantities of water, and the general measures usually employed in the presence of fever. If these fail, specific remedies sometimes prove beneficial. Another form of tox-

emia, which is associated with dehydration, is characterized by nausea, vomiting, a high level of blood-urea and frequently by acidosis. This may respond to the intravenous administration of large quantities of fluid. An effort should be made to keep the kidneys active. The hemorrhagic type of toxemia is characterized by anemia and calls for transfusion of suitable blood, or intravenous infusions. Calcium is also commonly used intravenously, but is often of no avail.

TREATMENT IN RELATION TO STUDIES OF FUNCTION

Functional studies of the liver have not as yet affected the treatment of disease of the liver to any considerable extent. They do, however, affect judgment as to the type of treatment to be adopted. They reveal the extent of the functional injury, the course of the disease, and hence they offer some index to the seriousness of the condition, the urgency for interference and the extent of the surgical risk. Thus, splenectomy in the presence of high grade retention of dye carries an extremely high mortality. The functional tests reveal the effects of treatment, particularly of surgical procedures, for the relief of obstruction, the effects of measures, for the relief of congestion, and the effects of specific remedies, such, for instance, as antisyphilitic drugs used in cirrhosis due to syphilis. They are still complementary to clinical study of the patient.

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CHAPTER XL

ACUTE MASSIVE ATELECTATIC COLLAPSE OF THE LUNGS.

Norman B. Gwyn

Definition.—This illness consists of more or less acutely progressive collapse of a lung or large part thereof; it may be looked upon as often merely a more extensive process than the well-known patchy collapse. It differs from other forms of gross collapse in existing without coexistent pneumothorax and in producing a marked increase of the intrapleural negative pressure. As met with in clinical medicine, it seems to be an associate of most of the acute thoracic affections or an accident consequent upon many surgical procedures, particularly operations upon the abdomen. It is perhaps most frequently met with as a result of blocking of the air passages by foreign bodies and as an interesting complication of chest wounds. Much of the uncertainty as to its method of arising has been dispelled by the accurate work of the bronchoscopists who have demonstrated that obstruction of the air passages stands in intimate relationship with both the patchy and the massive collapse. Weakness and shallowness of the respiratory activities is to be looked upon as the underlying cause of collapse in the cases not directly due to the impaction of foreign bodies in the trachea or bronchi.

Descriptive History and Etiology.—Apneumatosis was a familiar picture to the clinicians of seventy-five years ago. Collapse of the lungs as a complication of bronchitis was described by Legendre and Bailly, in 1846, and again by Gairdner, in 1851; the latter writer suggested the "ball-valve theory" as an explanation of the process at work in the production of acute atelectasia. In 1860, Barthels declared that diphtheria of the bronchial tubes was regularly followed by extensive collapse of the lungs. Jürgensen and Lichtheim seem to have determined the cause of acute collapse of the lungs in a most conclusive manner, the former suggesting that the air imprisoned in the lung alveoli beyond a created obstruction was absorbed by the circulation, and the latter actually demonstrating the rapidity with which the various gases and air may be taken up by the blood passing through the lung tissue. Lichtheim also showed that if the vessels going to the lobe beyond the obstruction were ligated, there was no collapse. Pearson Irvine and William Pasteur, returning to the subject many years later, attributed massive collapse to paralysis of the diaphragm and the muscles of respiration, instancing the atelectasia found in some of their

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diphtheria cases, when these muscles had been affected by the diphtheria toxin. Pasteur's later contributions, however, in which he describes "active massive collapse" as a postoperative pulmonary complication, and the experimental work of Elliot and Dingley, may be said to have resurrected the long buried knowledge of the existence of this unusually interesting condition, for beginning in 1914 [1] many important articles appeared, indicating that the surgeons at least were aware of the fact that after abdominal operations and after wounds of the chest a massive collapse of the lung might be expected to occur. Some of the various theories which have been put forward to explain the nature of this acute atelectasia have been touched upon, but at the present moment it would seem that the question has been well decided by the work of Jackson and his collaborators who insist that in every case of collapse there is obstruction of some form in the air passages. The frequency with which these workers have found an actual obstruction with coincident collapse inclines one to the belief that in the early stages of the accident at any rate, there will always be found some actual accumulation in the bronchi or bronchioles. Coryllos and Birnbaum, by their careful experiments, have completely substantiated the findings of Lichtheim which seemed to indicate that massive collapse was the result of bronchial obstruction plus the absorption by the circulation of the imprisoned air.

Anatomical and Clinical Associations.—In fatal cases of complete collapse the lung is found absolutely airless; there is, however, no fluid or air in the pleural cavity; an obstruction of some nature is usually in evidence. In some cases, at autopsies, no actual plug or foreign body has been detected in the bronchus leading to the atelectatic area. It is probable, however, in instances of this sort, that increased secretions, hampered respiratory movements, inability to cough, with coincident inflammatory narrowing of the bronchus, have given enough cause to produce complete obstruction. With progressing collapse, as the air in the alveoli is absorbed, the intrapleural negative pressure increases, the chest wall falls in, the diaphragm rises and is held in a fixed position; in a unilateral collapse the trachea, heart and mediastinum swing over to fill the vacuum and will remain displaced into the side of the collapsed lung till reëxpansion takes place. The extreme degree of negative pressure produced by the absorption of air from the alveoli is probably the cause of the diaphragm remaining high and fixed; actual paralysis of this muscle is a rare association with collapse and, with removal of obstruction, the diaphragm at once begins to function.

Chiefly associated with operations upon the abdomen, acute atelectasia has been most often met with in the surgical clinics; it is, however, an accident to be anticipated in any chest wound and one to be looked for in

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[1] Bradford, Crymble, and the majority of the references from 1914-1926.

many of the better known disorders affecting the chest and its contents. It has been described as occurring in the course of pneumonia, bronchitis, pulmonary tuberculosis, and abscess of the lung; furthermore, as complicating effusions in the pleura and pericardium; and, finally, as associating itself with pressure on the bronchi from without, or with the impaction of foreign bodies in the airways. Any exhausting illness, any of the conditions which interfere with free movement of the diaphragm and an active cough reflex, will predispose to a massive collapse. In any case of acute atelectasia of obscure origin such details should be carefully considered, for interference with the ventilation of the lung bases, as in shallow respiration, and inability to remove gathering secretions as a result of incomplete cough frequently initiate the process.

Pathological Changes.—The lung is absolutely airless and sections show no sign of alveolar structures. In cases where death has been a matter of minutes only, there will be no sign of inflammatory reaction; some blood may be seen in the bronchioles and the blood-vessels are engorged. In the more slowly developing instances of massive collapse the signs of a coincident bronchitis and bronchiolitis are in evidence. In the "foreign body" cases, a type in which there is often considerable irritation, there may be added an edema of the structures which has given them the name of "drowned lung."

Symptoms and Physical Signs.—The symptoms are those common to many of the acute disorders of the lungs and circulation. Large areas of collapse, however, may exist without evoking distress. Dyspnea of greater or lesser degree, depending usually upon the extent of the collapse and the rapidity of its onset, will be seen. If an inflammatory condition of the lung coexists, some pleural pain may be expected, but, as a rule, chest oppression rather than acute pain is complained of. There may be expectoration and fever corresponding more with the exciting cause, such as bronchitis or lobular pneumonia, than with the actual process of collapse. There is usually a rapid rise in the pulse rate; cough belongs more to the early hours of the progressing atelectasia and, after the patient has accommodated himself to the limitation of his air space, may completely disappear. Bloody sputum is not the rule; what sputum there may be must come from parts other than the collapsed areas and is simply that type so regularly seen with catarrhal affections. Cyanosis develops quickly and may be of extreme degree; in a few hours, if the case is to progress favorably, the dyspnea lessens, though the area of collapse may remain unchanged. With dislodging of the obstruction, all symptoms may quickly cease; reëxpansion of the lung and recurrences of the collapse may take place during the course of several weeks; it is unusual to see return of respiratory urgency in such cases. Delayed resolution of a pneumonic process may be an expression of collapse. In the author's cases pleural pain was never in evidence. The most acute dyspnea occurred in the post-

operative cases. In one of the chest wound cases there was no distress after the first few hours, even though the collapse had affected one whole lung and large areas of the other. The physical signs of massive collapse are striking. The chest wall sinks in over the collapse. The difference in the two sides of the chest is very apparent in the unilateral lesions. The unaffected side usually appears over-distended: the ribs can be seen to have fallen in, the heart may be beating well over on the right side when the right lung is collapsed, or in the left mid-axilla when the collapse affects the left base. Collapse of either apex displaces the heart upwards. The expansion of the affected side is nil. The patient tends to lean towards the affected side of the chest. Further indication of the degree of negative pressure produced by the collapsing of the lung is seen in the deep indrawing of the intercostal spaces. The plugging of the bronchi by secretions or foreign body diminishes the vocal fremitus. As might be expected, should the plug be removed, the vocal fremitus may return with increased force while the lung is still collapsed. Variations in the degree of obstruction are responsible for the many different reports on the physical findings. The same lung or the same lobe may give utterly different physical signs in the course of the day depending upon the size, position and quality of the obstruction. The collapsed lung is solidly dull to percussion; the overexpanded parts of the lungs are hyperresonant and may suggest a pneumothorax. Traube's semilunar space retains its resonance as the diaphragm is lifted high; the liver area will appear to have ascended. Indications of aëration of the lung will be seen in the return of any quality of resonance. The absence of the normal areas of heart dulness may be a striking feature when the collapse affects the right side. The heart and the mediastinum when displaced into the collapsed side may materially contribute to the solidity of the dulness. On auscultation the same remarkable variation as noted in connection with palpation, must be looked for. With complete blocking of a bronchus, and with the diaphragm held high by the increased negative pressure, it is unlikely that sound vibrations will be conveyed into the collapsed area, nor is it likely that any expansion of alveoli will take place. Hence absence of breath sounds, absence of voice sounds, is the common finding in the early hours of massive collapse. With a collapse of a whole lobe or whole lung the solidified tissue may conduct sounds from underlying large bronchi, and tubular breathing with bronchophony may be heard. The early crepitant râle of pneumonia has no place amongst the physical signs of collapse. With loosening of obstruction, sounds or vibrations will begin to come through to the ear and, while the lung is still carnified, may have a tubular quality. Many variations in the quality of the sound have been noted. With beginning air entry and passage of air through secretions, moist râles may be heard. The variations of the auscultatory signs have been closely correlated by bronchoscopy with the shifting of obstruction in the air ways.

The X-ray findings have substantiated the surmises as to what was going on in the chest. At times the blackness of the shadow obscures everything save the displacement of the mediastinum. This density of shadow may be due to engorgement of the capillary circulation. In well-marked cases the drooping of the ribs on the affected side is well shown, the fixation of the diaphragm in an elevated position is evident, and the swinging of the heart and mediastinum into the collapsed area with deviation of the trachea is most apparent. The heart shadow may completely disappear from one or the other side of the chest. Under the fluoroscope the fixation of the diaphragm can be well appreciated, and frequently, with shifting or removal of the obstruction, the aëration of the lung can be followed as well as the beginning movement of the diaphragm.

Diagnosis.—In the typical cases of some hours' standing, signs of consolidation, sinking of the chest wall, deviation of mediastinum and trachea towards the consolidation, and elevation of the diaphragm make a definite picture: only old cases of fibrosis of the lung can resemble the condition in any way. Collapse should be thought of in connection with any chest wound, with any affection of the air passages, of the lungs, pleura and mediastinum, and with any postoperative pulmonary accident. A unilateral consolidation of the lung, subsequent to an operation, should always suggest collapse, since postoperative pneumonias are usually of bilateral distribution. Displacement of the heart and mediastinum towards a consolidated area in the chest, which has developed acutely, is always an expression of collapse. From a large pneumonic consolidation, collapse would be distinguished by the displacement of the organs toward the consolidation. From effusions in general, collapse will differ in so far as effusions push down the diaphragm and liver, and displace the mediastinum towards the unaffected side. The physical signs of collapse, however, may at times suggest either consolidation or effusion. Sudden collapse of a lung area may occur in the course of many pulmonary and pleural affections, and should be considered with the development of any unexplained urgency. Collapse of the left lung base is an almost regular accompaniment of pericardial effusions. A developing collapse of the lung may have to be distinguished from the various acute cardiac accidents, from embolism, fat embolism and other postoperative complications involving heart and lungs. The detection of an area of consolidation with the subsequent displacement into the consolidation of the chest contents is the essential part of the diagnosis, for the symptoms of chest oppression, cyanosis, dyspnea and rapid heart action are common to all.

Prognosis.—The prognosis depends in large part upon the associated conditions. Recovery may take place when most of a patient's air space has been obliterated. Death in four cases reported by Ball,[2] where only the

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[2] Ball, *Arch. Path.*, May, 1928.

bases had been collapsed, must be considered unusual; tracheotomy had been performed in each instance and the laryngeal nerves had been injured by thyroidectomy.

Treatment.—Urgent as the symptoms of this lobar-like collapse of the lung may be, the evolution of our knowledge of its etiology has pointed out methods for its treatment, which in many cases seem to work in an almost dramatic manner. It is probable that much can be done to prevent the development of a massive collapse in those patients who have been subjected to operations under general anesthesia and again in those patients who for various reasons are compelled to lie supine for long periods of time; it is not so likely, on the other hand, that much can be done to forestall the accident in the chest wound cases, or in those cases in whom the collapse seems to be associated with paralysis of the muscles of respiration, with trauma, with effusions, or with the many infections of the chest and its contents. The collapse once established and not too quickly progressive seems to be amenable to certain direct methods of treatment: The therapy of massive collapse then would appear to consist of both preventive and specific methods.

Preventive Therapy.—Since accumulation of secretions plays an important part in the blocking of the air passages, which eventually leads to the development of collapse, the prevention of this accumulation must be sought for in any case where poor aëration or ventilation of the lungs is likely to ensue as a result of limitation of the activity of the muscles of respiration. We must anticipate the occasional occurrence of a massive acquired atelectasia in any surgical operation, particularly if this operation be associated with abdominal incisions and with tight bandaging of the abdominal or thoracic parietes. If a general anesthetic has been administered, this anticipation must be the more active, because it is doubtful that any heavily anesthetized patient comes off the table without some increase in his bronchial secretions. If it has been necessary to administer morphin or a sedative drug which may unduly depress the cough reflex, and if the patient is going to require prolonged rest on his back, the anticipation is even more apt to be realized. In other words, the preoperative and postoperative care, which already has so much with which to concern itself, must include detailed directions which shall lead to the preserving of the greatest freedom of respiration possible under the circumstances, to the prevention of undue irritation of the bronchial tree, to the removal or at least to the shifting of retained secretions from the lower lying portions of the lungs. The accomplishment of these aims must be sought for by the avoidance of tight restricting bandaging about the abdomen and chest, by the utmost care in the giving of the anesthetic, by the use of a suction apparatus for the removal of secretion from the pharynx, by postural drainage while the patient is still unconscious, and, if permissible, by frequent turning of the patient from side to side so

that he may ventilate and free first one lung, and then the other. As an accessory perhaps in the preventive treatment, atropin may be given, if the tendency to bronchorrhea seems pronounced. The cough reflex must not be unduly depressed: morphin and its allies must be given warily at first. Since circulatory weakness and depletion of the body fluids may lead to a state of increased viscosity of the blood which in turn may perhaps invite thrombus formation, it will be wise to uphold the patient's strength by all appropriate means.[3] To-day it is recognized that preoperative purging and starvation is poor preparation for the shock which is to be undergone. A sufficiency of both rest and food, before and after operation, is perhaps the best circulatory stimulant. A current of cool air on the face incites the well-known reflex of deep inspiration and may be looked upon as a very sensible aid in any line of treatment directed against the development of a massive collapse. Elaborating this natural method of promoting ventilation of the lung, Scott and Cutler urge that all patients operated upon under general anesthesia should be given hyper-ventilation by breathing a mixture of carbon dioxid and oxygen at the end of the operation. They also urge that periods of deep breathing should be encouraged at frequent intervals during the first twenty-four hours after operation. If, after the operation, the signs and symptoms of shock are threatening, then all methods of stimulating the circulation should be employed, for an added congestive edema of the lungs must be avoided. Digitalis, pituitrin, adrenalin may at this time be of service. It is doubtful if preoperative digitalization has proved its worth. An important detail in the prevention of postoperative lung conditions is the keeping down of abdominal distention and, since interference with the diaphragm's action will materially hinder the aëration of the lung bases, it is probable that extreme distention will actively predispose to the acquiring of pulmonary collapse. The proper use of laxatives, of enemas, of pituitrin or eserin is indicated if such distention threatens, together with that form of diet least likely to produce flatulence, and if need be, the application of stupes to the abdomen. In seeking ways and means to prevent the development of massive collapse of the lung in the other many and various conditions in which it has been noted to occur, we are essentially limited in the line of our approach. Some of the details of preventive treatment as applied in the surgical cases are applicable; the lung bases should be carefully examined in any case whose illness or convalescence is long; the frequent turning of the typhoid patient from side to side in order to forestall pulmonary congestion has long been insisted upon. It is possible that in certain of the catarrhal conditions those drugs which liquefy secretions, such as the iodids, ammonia and squills, may serve a distinct purpose.

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[3] Just how large a part embolism and infarction may play in the production of collapse, it is difficult to say; in the light of Lichtheim's experiments one doubts any frequent association.

Direct Treatment of Massive Collapse of the Lung.—In a patient under observation some five years ago we noted, following on the puncture of the chest and the turning or moving of the child while taking his radiograph, that the lung immediately began to clear, and that in a minute, an upper lobe which had collapsed during the patient's pneumonia five weeks previously, and which had remained so, became distinctly aërated. The supposed unresolved pneumonia of the lower lobe disappeared in turn, in the matter of seventy-two hours. This was probably the first application of one of the direct methods of treatment of pulmonary collapse. It might be added that no fluid was obtained in the exploratory puncture. In our next case, one of pericardial effusion, the dyspnea precluded an attempt at ventilation by this method. Early in 1927 Sante noted the rapid expansion of the collapsed lung as a result of turning the patient to the unaffected side; he was able to repeat the performance on several occasions and from his reports it seems that he has discovered a most valuable and practicable method of treatment. In one of his cases he notes that a few cubic centimeters of tenacious sputum were brought up immediately after his turning of the patient. Sante is of the opinion that no other form of treatment is necessary, save in the cases which result from impaction of a foreign body in the air passages.

The treatment of the massive collapse of the lung, which Jackson tells us is an almost constant concomitant of firmly placed obstructing secretions, or of foreign body impaction in the air passages, is by the direct removal of the offending obstruction and the accumulated secretions through the bronchoscope. The reports from Jackson's clinic suggest that, as a result of the application of bronchoscopy, we have obtained not only a much clearer idea as to the cause of massive collapse of the lungs, but that we have arrived at the rational way of treating it. From the many hundred cases of collapse which have come under the observation of Jackson and his coworkers, it seems more than ever probable that plugging of the bronchioles and bronchi with tumefaction and cohesion of their walls is the one proven cause of massive collapse, and that the removal of obstructing secretions with its immediate betterment of the condition is the method of treatment to be preferred, if a skilled bronchoscopist is available. One can best refer to the many publications of Jackson, Jackson and Lee, Manges, Clerf, and others, to recognize the great value of bronchoscopy in cases of massive collapse due to the better known conditions in civil life. It will be interesting to see how applicable bronchoscopy will be in the massive collapse seen in association with wounds of the lung, and even in those cases where it has been assumed that some reflex action started the chain of events which finally collapsed the lung. It is probable that before long there will be on record details of such cases examined and treated by bronchoscopic methods; one will then be allowed to speak more authoritatively upon the subject. There is no drug treatment that

can be recommended when the collapse is once established; it would seem reasonable to administer oxygen freely, and if possible, to the point of relieving the cyanosis. After arriving at a state of complete atelectasia, there would be no occasion to administer carbon dioxid and oxygen, as has been spoken of in connection with the preventive treatment; in a conscious state the patient will probably practice deep breathing without artificial incitation. Care should be taken not to give anything that by its action would depress the respiratory center.

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There is an excellent article by Ball in the *Archives for Pathology* for May, 1928, describing massive collapse of the bases of the lungs in four cases dying after thyroidectomy. In all these cases the recurrent laryngeal nerve had been injured and tracheotomy had been performed. There was no firm obstructing plug in evidence but under the circumstances an accumulation of secretions must have taken place.

Articles by Manges and by Holmes in *Am. J. Roentgenol.,* 11, 1924, give a comprehensive account of the X-ray findings. Sante, *Radiology,* 1927, has an unusually good summary with reports of three cases.

CHAPTER XLI

BRONCHOSCOPY IN THE TREATMENT OF PULMONARY DISEASE

Chevalier Jackson and Chevalier L. Jackson

One of the most important developments in the study of the problems of the diagnosis and treatment of pulmonary diseases is the perfection of bronchoscopic technic to the point where its aid may be requested with no more hesitation than the clinician feels in asking for a serologic test or an intravenous medication. In fact a reaction such as is often seen after the latter is unknown after a skillfully done bronchoscopy. Many patients who have had both have volunteered the statement that as between them they dreaded only the intravenous administration of arsphenamin.

In the diagnosis of pulmonary disease we have had the internist who taps, looks and listens on the outside; the roentgenologist who looks through the patient; to these has been added the bronchoscopist who looks inside the patient.

In principle bronchoscopy is a specular examination. The technic, however, requires training and a trained organization. Even a trained endoscopist cannot do good work without two trained assistants. Such a team can do a diagnostic bronchoscopy without anesthesia and without danger to the patient in a few minutes.

The Defensive Powers of the Lungs.—In addition to the defensive powers against bacterial invasion possessed by all tissues in the body, the lung has two special means of defense, the cilia and the cough reflex. These two means of defense are efficient only so long as there is no interference with ventilation and drainage. Unfortunately, once the invading host gets past the first two lines of defense, these two lines in the involved area become impaired in efficiency because there is, necessarily, interference with ventilation and drainage. This creates a vicious circle which is fundamental in the etiology of all diseases of the lung. It is fundamental in the rapid progress of the acute condition; it is fundamental in the drifting of the acute into a chronic condition.

Bronchoscopic Aspiration.—The efficiency of bronchoscopic aspiration depends upon its great effectiveness in restoring the defensive power of the lungs. Though marvelous, often brilliant, in its results, the explanation is quite simple. The factors in the mechanism of the restoration of the defensive power are these:

1. The overwhelming load of work is taken off the cilia.

2. The thick tenacious pus and secretions that the cilia cannot waft are removed.

3. Stagnation is stopped. Stagnant pus becomes intensely irritating by decomposition; irritation results in mucosal swelling; swelling of the mucosa mechanically clogs ciliary wafting. Continuance of stagnation results in destruction of the cilia; later in destruction of the epithelium; later still in obstruction of the lumen of the airway by adding the bulk of granulations to that of the swollen mucosa of the bronchial walls. It takes very little addition to the thickness of the lining of a tubal wall to diminish the practical lumen of the tube.

Bronchoscopic Removal of Bronchial Obstruction.—*Granulations* are obstructive in three ways:

1. They have no cilia, consequently there is a gap in the ciliary transmission; the cilia below cannot waft pus across the gap.

2. The rough, irregular surface of the granular area retards the flow of secretions from below, whether propelled by cilia or by cough.

3. The granulations by their bulk diminish the lumen, and soon they obliterate it by meeting in the transverse axis of the tube. Granulations that are exuberant are easily removed by pinching them off with bronchoscopic forceps under guidance of the eye. They are soon replaced by small, firm, bright red granulations. In most cases removal is not necessary; stoppage of stagnation by bronchoscopic aspiration, alone, will often result in a flattening of the granulations and their replacement by the small firm type that are the forerunners of epithelization.

Bronchial obstruction may be due to *secretions;* they may be so dry as to require the bronchoscopic forceps for removal; if fluid, however thick, they can be aspirated by the powerful negative pressure of the electrically driven aspirating pump. In *fibrinous bronchitis and tracheobronchial diphtheria,* membranous casts may become as obstructive as a foreign body; then they require removal with bronchoscopic forceps.

Pulmonary Abscess.—One of the greatest aids to the treatment of this serious condition discovered in recent years is that the pus, in many cases, can be harmlessly and quite efficiently drained through the mouth by bronchoscopic aspiration without anesthesia. Endobronchial medication is, for the bronchoscopist, mechanically easy of performance, but it is from the restoration of the defensive powers of the lung by the stoppage of stagnation that the remarkable results of bronchoscopic treatment are obtained. As with any other form of treatment the results are best in single abscesses of recent origin and uncomplicated by bronchiectatic conditions. In many such cases the results are remarkable. If the suppurative process is extending toward the pleura but has not yet reached it, there is a good chance of arresting progress; but if the pleura is already reached it is too late; the disease has progressed beyond the limits of bronchoscopy. The pleura can-

not be efficiently drained through the mouth. In treating pulmonary abscess it is of the utmost importance to recognize the fact that bronchoscopic drainage is only an adjunct to general medical management. The patient must not be allowed to consume all his gain by increased physical activity. If not actually bedfast he should rest sixteen, eighteen or twenty hours in bed; and this should be under outdoor conditions. It is important that spontaneous drainage be not interfered with by antibechics. The prevalent use of opiates to check or abolish the cough reflex, the watchdog of the lungs, is most illogical and is certainly a great mistake. The purpose of cough in these cases is drainage. To paralyze the cough reflex with opiates is to promote stagnation. Unsuspected foreign body is always a possibility in every case of pulmonary abscess no matter how clear the history of influenzal, pneumonic or other origin may be (Jackson, *Brit. M. J.,* Oct. 17, 1925).

Posttonsillectomic Pulmonary Abscess.—In recent years pulmonary abscess as a postoperative complication of tonsillectomy has been recognized as one of the most serious sequelæ of this operation. The child becomes ill, usually within the first week after operation. Cough, fever, and foul, sometimes bloody, expectoration are the usual symptoms. The Roentgen diagnosis is conclusive (Fig. 1). Bronchoscopic aspiration is quickly curative in fully 80 per cent of the cases if resorted to early. The temperature, pulse and respirations drop to normal after a few aspirations, often after the first one. After the condition has become extensive, multiple and chronic, bronchoscopic aspiration is usually indicated, but the results, as with any other form of treatment, are not so good. It cannot be too strongly urged that bronchoscopic aspiration be used at the earliest possible moment after the onset of symptoms.

Bronchiectasis.—The extent and degree of bronchiectasis can be more accurately mapped by bronchoscopic pneumonography than by any other method of making a pneumonograph. If the disease is limited to one lobe it will usually yield to bronchoscopic aspiration. If extensive, bilateral, of long duration, and accompanied by expectoration of very large quantities of pus, a long series of treatments will be required and the favorable results will be fewer. The bronchoscopic aspirations are done about twice weekly without general anesthesia. The concurrence of a focus of infective disease in the nasal accessory sinuses or elsewhere must be searched for and eradicated. In every case of bronchiectasis, foreign body should be excluded by bronchoscopy. In many cases at the bronchoscopic clinic an unsuspected foreign body has been discovered and removed at a bronchoscopy from a patient referred for bronchiectasis supposed to be of other origin (Jackson, *Brit. M. J.,* Oct. 17, 1925). The great difference is in the prognosis. Bronchiectasis of foreign body origin will usually get well quickly and spontaneously after bronchoscopic removal of the foreign body; whereas the same extent and degree of pathology of other origin usually requires a
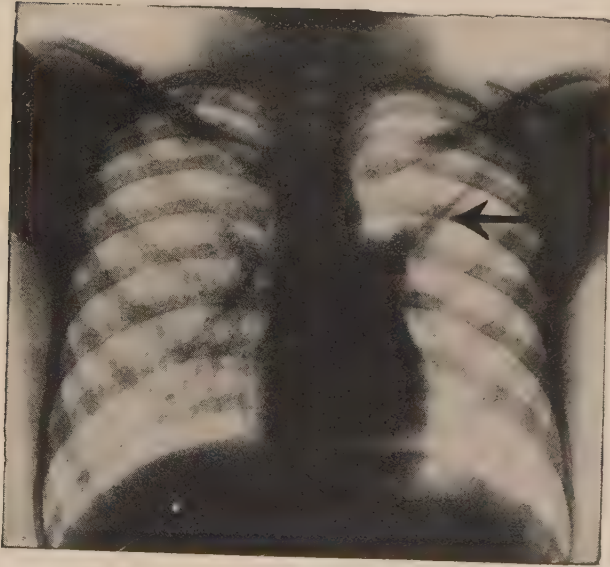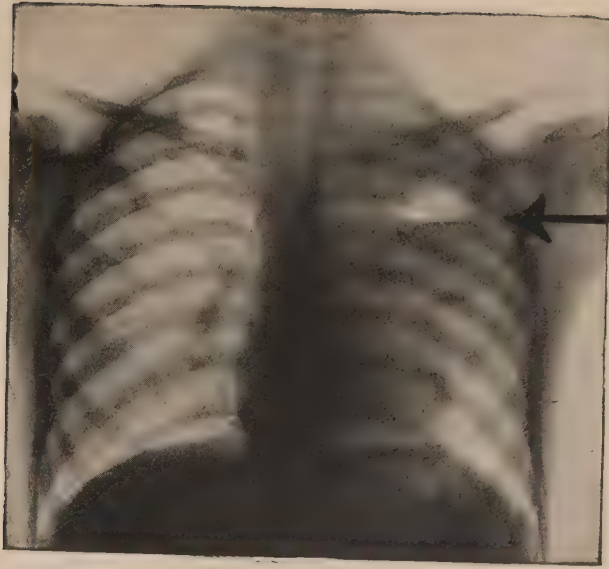
FIG. 1.—POSTTONSILLECTOMIC PULMONARY ABSCESS.

In the upper illustration an abscess with a fluid level is shown as developed three weeks after operation, in a boy aged nine years.

The lower illustration shows the complete disappearance of the abscess, five weeks later as the result of ten bronchoscopic aspirations. (Courtesy of W. B. Saunders Co., Philadelphia.)

prolonged series of bronchoscopic aspirations to cure and has very little if any tendency to spontaneous recovery.

Vaccine Therapy.—Vaccines obtained from sputum often have little value because of oral contamination of the specimen. Uncontaminated specimens can be obtained directly from the lesion, by bronchoscopy, in a few minutes, without any anesthetic, general or local. The patient may thus get all the benefit possible from vaccine methods of treatment.

Hemoptysis.—The source of bleeding can often be determined by diagnostic bronchoscopy. It may be found in a tuberculous lesion, an abscess cavity, an angioma, a gumma, a varix, a granuloma, or a cancer. Before doing a diagnostic bronchoscopy on a patient with hemoptysis, organic cardiac disease and aneurysm should be excluded as the source of blood.

Pneumonia.—Lobar pneumonia is, in some cases at least, simulated by an atelectasis due to obstruction of a bronchus by mucous exudate. As shown by Coryllos and Birnbaum (Jackson, *New England M. J.,* Oct. 10, 1928) this condition is quickly relievable by bronchoscopic aspiration.

Broncholiths.—Lung-stones are occasionally removed from the bronchi by bronchoscopy. The technic is the same as for foreign body.

Tuberculosis of the Lungs and Tracheobronchial Tree.—Tubercle bacilli have often been found in secretions removed through the bronchoscope when the sputum has been negative. Guinea-pig inoculations are of especial value when this directly obtained uncontaminated material is used. There are a few cases of pulmonary tuberculosis with bronchial stenosis and stagnation of pus that call for bronchoscopic aspiration of the pus and bronchoscopic treatment of the stenosis. The stenosis may be due to fungations, tuberculomata, or swelling; or it may be cicatricial. Fungations and tuberculomata are readily nipped off; the cicatricial lesions may be dilated (Fig. 2). Obstruction and stagnation cause fever from mixed infections in the tuberculous, just as they do in the non-tuberculous, and they call for the same relief measures. Bronchoscopic aspiration is quite efficient in such cases. Tuberculosis of the bronchial wall may be treated with chaulmoogra oil, as advocated by Lukens for tuberculous lesions of the larynx. Care is necessary in all local applications to the bronchi. Applications should never be in flooding quantities and should never be irritating.

Influenzal Laryngotracheobronchitis.—If severe this is associated with croupy cough and dyspnea calling for a diagnostic bronchoscopy. In some cases bronchoscopic aspiration is needed; in most cases, however, the violent paroxysms of coughing and the inflammatory conditions subside quickly when the tracheal secretions are alkalinized by the internal administration of sodium bicarbonate.

Chronic Tracheitis.—This is characterized by chronic cough and the occasional expulsion of small balls of thick, gelatinous "moss-agate" (Jackson and Coates' *Textbook,* W. B. Saunders Co.) tracheal sputum; the

grayish streaks look like soot mixed through the secretion. On bronchoscopy the tracheal mucosa is found chronically inflamed. The best treatment is residence in a warm, moist, sea climate. If this is impossible avoidance of dust is imperative and local treatment with a solution of 1 per cent monochlorphenol in liquid petrolatum is indicated.

Fibrinous Bronchitis.—The bronchoscope is occasionally called for to remove fibrinous casts that are acting as a foreign body.

Tracheobronchial Diphtheria.—Bronchoscopic removal of polyp-like masses of fresh fibrinous exudate or, at a later stage, casts of membrane
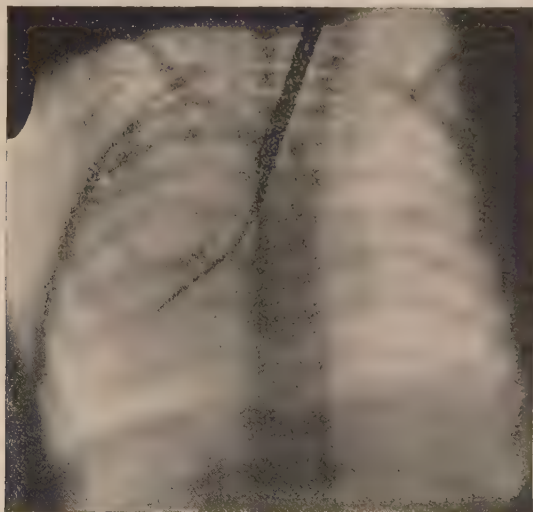
Fig. 2.—Bronchoscopic Dilatation of a Congenital Web-Stenosis of the Left Main Bronchial Orifice That Was the Cause of Suppurative Disease of the Left Lung.

A number of bronchoscopic dilatations resulted in complete cure. Film made by Willis F. Manges. (Courtesy of W. B. Saunders Co., Philadelphia.)

may be called for. Bronchoscopy is indicated when diminished breath sounds and an impaired percussion note indicate bronchial obstruction.

Congenital Stenosis of a Bronchus.—Stenosis is readily discovered by bronchoscopy. This method of diagnosis is called for by physical signs of bronchial obstruction and Roentgen signs of atelectasis. Treatment by bronchoscopic dilatation is curative (Fig. 2).

Compression Stenosis of the Trachea and Bronchi.—Compression of the trachea is most commonly caused by goiter, substernal or cervical, aneurysm, new growths, or, in children, by enlarged thymus. Less frequently, enlarged tuberculous, leukemic, luetic or Hodgkin's mediastinal glands compress the air way. The left bronchus may be stenosed by pressure from a hypertrophied cardiac auricle. Compression stenosis of the trachea associated with pulmonary emphysema accounts for the dyspnea during

attacks of coughing. Any kind of bronchial stenosis leads to suppuration in the bronchi from stagnation of secretions and obstruction to ventilation; in other words, there is impairment of the defensive power of the lung. If the stenosis is causing a dangerous degree of dyspnea the bronchoscope not only reveals the cause; it is left *in situ* while tracheotomy is being done. A long tracheal cannula can be inserted to pipe the air past the compression. Treatment of the compression may then be safely begun according to conditions found. An enlarged thymus will usually diminish under Roentgen treatment; lymphoid growths may need radium treatment; other conditions may require bronchoscopic treatment; but air must be carried down to the lungs under the advice and care of the bronchoscopist.

Bronchial stenosis may be comprehensive, neoplastic, inflammatory or cicatricial. Only the last remains to be considered. Cicatricial stenosis is revealed by bronchoscopy and yields readily to bronchoscopic dilatation under guidance of the eye. The basic disease, if tuberculous or syphilitic, calls for general treatment. Below a stricture there is always pus, and this must be aspirated.

Benign Growths.—In the lumen of a bronchus benign growths cause interference with ventilation and drainage, often resulting in atelectasis and suppuration. They can be diagnosticated only with the bronchoscope (Willy Meyer). Bronchoscopic removal causes prompt subsidence of the suppuration, which has been due to obstructed drainage and aëration. A number of the patients with benign bronchial growths have come to the clinic with an erroneous diagnosis of asthma. In these cases all asthmatic symptoms have disappeared after bronchoscopic removal of the growths.

Cancer of the Lung.—The bronchoscope affords the only means of early and positive diagnosis of primary endobronchial cancer (McCrae, Funk and Jackson). The less common form starting in the periphery can be diagnosed by the bronchoscope as soon as it becomes endobronchially manifest. In both classes of cases bronchoscopic biopsy gives the absolute certainty required for lobectomy, Roentgen or radium treatment. In many cases at the bronchoscopic clinic early bronchoscopic diagnosis and deep Roentgen therapy have arrested for a number of years histologically proven cancer of the lung. In many cases cancer of the lung is relatively a mild, slowly metastasizing form of malignant disease. In consultation with Henry K. Pancoast, the author has bronchoscopically placed radon seeds (radium emanation containers) in cancer of the lung. The bronchoscope affords means for great precision in the placement of the seeds (Fig. 3) by use of a specially devised "planter."

Asthma.—The diagnosis of asthma was formerly regarded as a very simple problem; the term was loosely applied to almost any pulmonary condition accompanied by a wheeze; but under the light of direct examination of the tracheobronchial tree by bronchoscopy it was soon discovered that the inferential diagnosis of asthma was very often erroneous. So often

did this happen that it has become a dictum of the bronchoscopic clinic that "all is not asthma that wheezes." In hundreds of cases nocturnal dyspneic attacks with wheezing have, on bronchoscopic examination, been found to be due primarily to such conditions as cicatricial stricture, compression stenosis, granulations, foreign body, thick secretion, crusts, exuda-

Fig. 3.—Roentgenogram Showing Radon Seeds Implanted in a Carcinoma of the Lung by Peroral Bronchoscopy.
(Henry K. Pancoast and Chevalier Jackson.)

tive membrane, benign growths, cancer. The differential diagnosis of these conditions can be made early and positively by the bronchoscope, and in most of them the bronchoscope is the only positive method of making a diagnosis. In all these conditions the bronchoscope is the means of treatment and in most of them bronchoscopic methods are curative.

In asthma, properly so-called, bronchoscopic aspiration is often curative of the attack. In other cases endobronchial applications are effective in arresting the attack. They are indicated in the cases that do not yield to ordinary remedial measures. The most useful remedies for endobronchial medication during the attack are cocain and adrenal preparations. To pre-
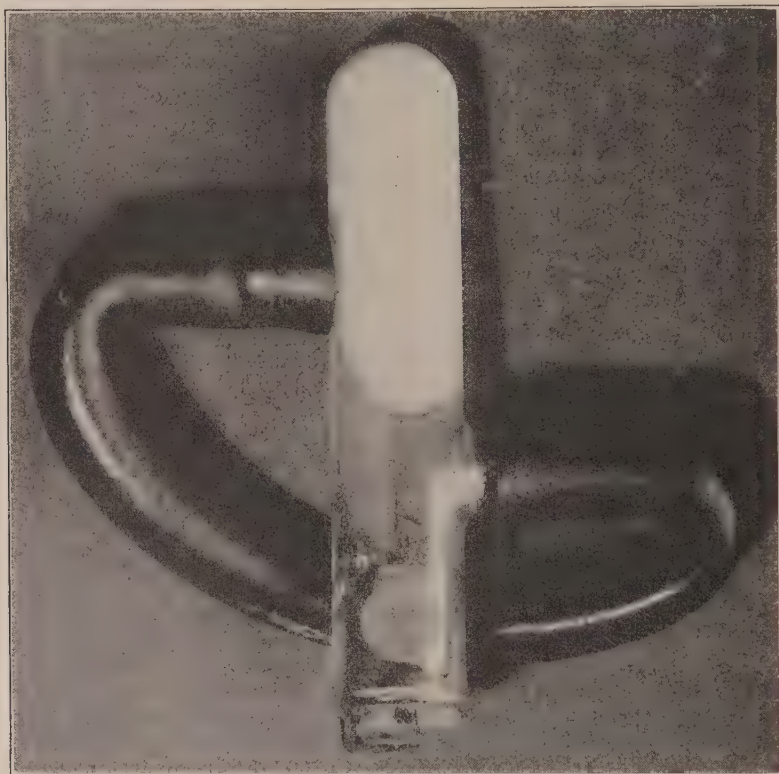
FIG. 4.—ILLUSTRATION OF A FUNDAMENTAL FACTOR IN SUPPURATIVE DISEASES OF THE LUNG.

The collecting tube of the bronchoscopic aspirator has been inverted but the pus is so thick that it will not run down. The patient had been coughing for hours but could not get this thicker part of the pus up. Thick, gummy, tenacious pus like this clogs the cilia to the point of total inefficiency. Stagnation of pus is the largest factor annihilating the defensive power of the lung. Bronchoscopic aspiration of the obstructive pus and secretions restores the defensive power of the lung. This kind of pus will almost always result in progressively increasing pathological changes in the lung unless removed bronchoscopically. John A. Kolmer found that this consistency was due to the presence of large amounts of fibrinogen probably of hematogenous origin.

vent the attacks bronchoscopic aspirations at biweekly intervals for a few weeks or months are helpful, in some cases curative. These are the cases associated with thick, tough secretions that the patient cannot expectorate (Fig. 4). This discovery has modified the conception of the pathologic mechanism of asthma and asthmatoid symptoms.

Blastomycosis of the Lungs.—Though this is not a common disease it is not so rare as might be supposed. The only way the diagnosis can be made with certainty is by the bronchoscopic removal of the fungating granulation tissue from the bronchial wall. The mycotic organisms may be found in the sputum, but they are difficult to find. The treatment by potassium iodid is quite efficient; small doses to begin with and increasing dosage up to 6 or 7 grams daily is a good plan.

Spirochetosis.—The presence of spirochetes in the mouth of many individuals renders it uncertain, in a given case, whether or not the finding
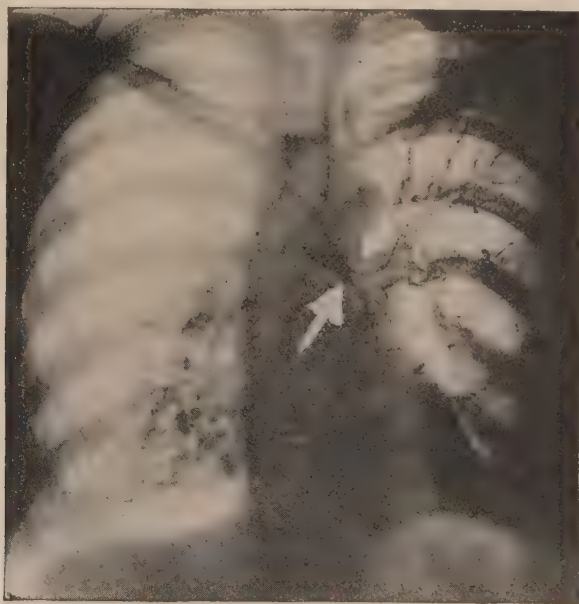
FIG. 5.—BRONCHOSCOPIC PNEUMOGRAM OF A WOMAN AGED 51 YEARS.

The pneumogram showing cicatricial stricture of a bronchus secondary to a suppurating mediastinal adenopathy 4 years before. The patient has remained well until influenza started suppuration below the stenosis. Patient cured by bronchoscopic aspiration and dilatation of the stricture. (Courtesy of W. B. Saunders Co., Phila.)

of spirochetes in the sputum is evidence of spirochetosis of the bronchi. The bronchoscope, by enabling the removal of specimens of secretions from the bronchi uncontaminated by oral secretions, gives the laboratory report absolutely positive or negative value. In addition to intravenous medication by arsenical preparations, arsphenamin diluted with normal salt solution may be applied locally through the bronchoscope.

Vincent's Infection of the Bronchi.—The presence or absence of Vincent's organisms in the bronchi can be determined with absolute certainty by examination of uncontaminated specimens removed bronchoscopically. The treatment is the same as advised above for spirochetosis.

Postoperative Atelectasis.[1]—This condition follows an operation, most often abdominal. It was at first called "postoperative massive collapse." It is essentially an atelectasis of the lung without pneumothorax. A main
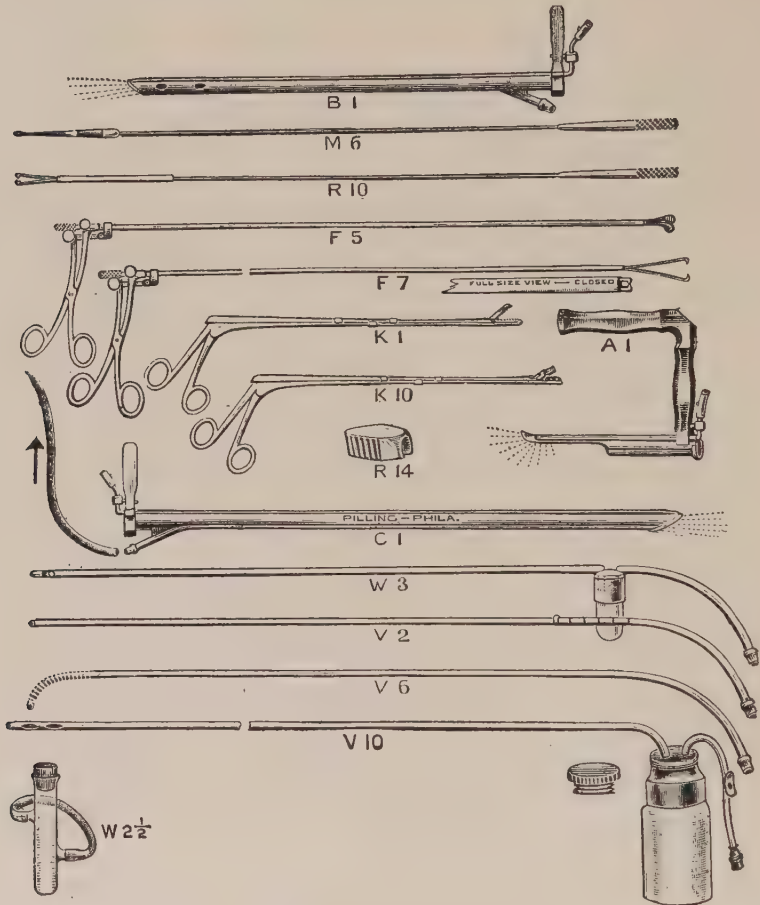
FIG. 6.—PERORAL ENDOSCOPIC INSTRUMENTS.

A1, Direct laryngoscope. B1, Bronchoscope. C1, Esophagoscope with aspirating canal. M6, Esophagoscopic bougie for safe dilatation under guidance of the eye. R10, sponge carrier for gauze sponges; the sponges are not shown but are absolutely essential—at least 4 dozen of the proper size for each size of tube to be used should be in readiness on the sterile table. F5, Esophagoscopic and bronchoscopic forceps. F7, Rotation forceps. K10, Laryngeal forceps for taking specimens of tissue; a longer form of this forceps is needed for bronchoscopic and esophagoscopic use. W3, Clerf collecting tube. W2½, Lukens specimen collector. V2, Aspirating tube with "warning stop." V10, Chevalier L. Jackson esophageal evacuator. V6, Spiral tipped aspirating tube. (Lynah.) R14, Moore thimble bite-block.

or large bronchus becomes obstructed, "corked" so to speak; the air in the tributary portion of the lung becomes absorbed, and the lung collapses.

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[1] See also chapter by Gwyn, page 490.

The negative pressure is satisfied, not by admission of air to the pleural sac, but by displacement of the mediastinal structures over toward the collapsed lung. If the obstruction is a plug of thick tenacious secretion (Fig. 4), its bronchoscopic aspiration will allow the collapsed lung to expand, and a prompt cure follows in almost all cases. The condition was formerly called postoperative or postanesthetic pneumonia. There is no pneumonic process; it was the misinterpretation of the physical signs that led to the error. The atelectasis, if unrelieved by spontaneous expulsion or by bronchoscopic removal of the plug, usually results in abscess because of the deficiency in the defensive power of the lung caused by the obstruction to ventilation and drainage. When the disease was thought to be pneumonic

FIG. 7.—PLANTER FOR PLACING RADON SEEDS IN CANCER OF THE LUNG.

The gold collar by screening the radiation permits of coöperation of the fluoroscopist with the bronchoscopist in the accurate placement of the seeds, if fluoroscopic guidance should be considered necessary. The eye at the tube is the best guide, but sometimes checking as to the relationship of the periphery of the growth may be desired.

the suppuration was considered a postpneumonic abscess. Bronchoscopy at the earliest possible moment will restore the defensive powers of the lung and will prevent abscess formation. If the obstructing plug of secretions is not removed death may follow quickly from similar occlusion of the other main bronchus; but more often the sequel is chronic pulmonary abscess. This condition is readily curable in its earlier stages by bronchoscopic aspiration and general medical management. In its later stages the abscess becoming large or multiple abscesses developing, external surgery is often required. The sequel, instead of abscess, may be bronchiectatic in character; if so, the same treatment is applicable and if not bilateral or of too long standing is equally effective.

Hypostatic "pneumonia" has been bronchoscopically shown to be not a pneumonia but an obstructive atelectasis, as explained in the foregoing paragraph. It is quickly relievable by bronchoscopic aspiration.

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CHAPTER XLII

THE THERAPEUTIC USE OF DIGITALIS

C. Sidney Burwell

Digitalis is a complex drug with a complex action and our knowledge of it and of its effects is far from complete. Certain recent studies (Harrison and Leonard; Burwell, Neighbors and Regen; Cohn and Stewart) have necessitated a revision of some earlier conceptions of the mode of action of digitalis and the precise mechanism is not yet the subject of general agreement. However, although the beneficial effects of digitalis are not entirely understood, enough has been learned from animal experimentation and the observation of patients for one to make a practical scheme for administering the drug to patients.

INDICATIONS FOR THE USE OF DIGITALIS

The beneficial effect of digitalis is most striking in heart failure [1] associated with the rapid irregular ventricular action usually observed in cases of auricular fibrillation. Digitalis, both by its direct effect on the muscles and by acting through the vagus nerve, diminishes the conduction ability of the tissues joining auricle to ventricle. By this action the ventricular rate is diminished, the filling of the heart is improved, and its rest period is increased, with a resulting favorable effect on the signs and symptoms of heart failure. In this instance the effect of digitalis on the heart is clearly a sedative one. When digitalis is given in such a case it should be given in doses sufficient to obtain the optimum pulse rate. This usually lies between 60 and 80. When auricular fibrillation is not accompanied by heart failure digitalis may be used to slow the rate of the ventricles in an attempt to prevent the development of symptoms of failure. In auricular fibrillation accompanied by a slow ventricular rate and cardiac failure a less dramatic effect on the symptoms of failure is to be expected from the drug. Under these conditions a high degree of heart-block already exists and therefore caution in the administration of digitalis is necessary lest the rate be depressed to a point below that which

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[1] When the term "heart failure" is used there is meant a symptom group usually including dyspnea (which may be of the paroxysmal type), engorgement of the neck veins, peripheral and pulmonary edema, and enlargement of the liver, and often including collections of fluid in serous cavities.

is desirable for the individual patient. It is essential to note that digitalis does not abolish the fibrillation of the auricles but has its effect on the heart rate only by diminishing the number of impulses reaching the ventricle. Indeed, auricular fibrillation may be produced by large doses of digitalis, particularly in patients suffering from advanced myocardial disease (Resnik).

Since digitalis does not abolish the arhythmia it is usually necessary or advisable to administer it continuously to patients with auricular fibrillation, for if the ventricular rate is allowed to rise again heart failure may appear. No ill effects are to be expected from the continuous administration of maintenance doses of digitalis, even over periods of years.

One exception to these general statements must be made. Certain patients have short paroxysms of auricular fibrillation. This occasionally occurs, for example, after operation in cases of thyrotoxicosis. When no symptoms of failure are present it is often better to wait for the end of the paroxysm, to use sedatives, or to attempt to restore normal rhythm by the use of quinidin, rather than to administer digitalis. Digitalis may possibly have the effect of prolonging the paroxysm. If the arhythmia persists after an interval of a day or two, or if it is felt at any time that the heart is being injured, digitalis can be given.

A similar effect upon a high ventricular rate may be seen when digitalis is administered to patients with auricular flutter, a condition closely· analogous to fibrillation. However, in auricular flutter the administration of digitalis is followed not only by a slowing of the rate and an improvement in symptoms but in a large percentage of cases by a disappearance of the abnormal rhythm itself (Lewis).

In congestive heart failure with normal rhythm the administration of digitalis is followed by a change for the better in a fair proportion of patients. The improvement in these cases is often less brilliant than in those just described, and tends to be less and less in successive attacks of failure. That digitalis is useful at all, beyond its effect on the rate of the ventricles in patients with fibrillation or flutter, has been denied. Recent studies, however, leave little doubt that in cardiac failure with edema and associated with a sinus rhythm of the heart, the drug may confer a definite benefit (Christian, Luten, Marvin). The precise pharmacological effect which determines this benefit is not clearly understood, but it is not due only to slowing of the rate, since this may or may not occur in these cases with regular rhythm. The degree of improvement has been observed to be slight in cases of heart failure due to rheumatic heart disease, slightly greater in cases due to syphilitic heart disease, and greatest in the cases associated with hypertension and arteriosclerosis (Marvin). Whether this is due to the type of mechanical disturbance associated with these varying types of disease, or to the condition of the muscle itself, is not yet established.

The specific indications for the administration of digitalis are then as follows: to control the rate in auricular fibrillation or auricular flutter, to abolish the arhythmia in auricular flutter and to influence cardiac function in some favorable but unknown manner in congestive heart failure. Valvular disease, cardiac enlargement, acute endocarditis, simple tachycardia, or hypertension, do not in themselves demand the administration of digitalis. It is important, however, to remember that heart failure may be of any degree and that it is not necessary or desirable to wait until its symptoms are fully developed before beginning the drug. Shortness of breath on mild exertion, nocturnal attacks of dyspnea or slight evening edema of the ankles, particularly in people with known cardiac disease, constitute adequate evidence on which to begin the use of digitalis. This point should be emphasized. When patients suffer repeated attacks of heart failure it is often observed that their response to digitalis or other therapy is less and less satisfactory (Christian). Heart failure itself is injurious and its prevention is therefore enormously important. The early recognition of impending failure and its prompt treatment by digitalis and other means may thus postpone or prevent the final collapse of the circulation.

DIGITALIS INTOXICATION

Digitalis is an extremely potent drug. Its therapeutically effective dose is close to the toxic dose. It is accordingly necessary to know exactly what signs or symptoms are to be interpreted as indicating excessive digitalization. Toxic effects are due to the same action of the drug which gives it value therapeutically. They are not to be avoided by using special preparations, since the only preparations which will not produce intoxication are inactive ones. Loss of appetite, nausea and vomiting are frequent symptoms of digitalis intoxication. It has been shown that these symptoms are produced reflexly by the effect of digitalis on the heart (Hatcher and Weiss). It is perhaps fortunate that this is the case since the nausea and vomiting may prevent the absorption of more of the drug and thus protect the heart against further injury. Since these symptoms are due to action of the drug on the heart itself and not to any irritative action on the stomach or intestines, they cannot be prevented by the administration of digitalis by a route other than the oral one. It is sometimes a question for nice judgment as to whether nausea in a given case is due to some cause associated with the congestion of heart failure or to the intoxication of digitalis. When loss of appetite develops and it seems clear that this symptom is caused by digitalis, the administration of the drug should be promptly discontinued. If it is continued until nausea and vomiting occur, these severe symptoms are apt to endure for days, to the possible injury of the patient. The nausea and vomiting caused by digitalis are not usually continuous but are frequently intermittent. The patient may have

periods of comfort, followed by recurrent attacks of nausea and vomiting. These symptoms are obviously not related to individual doses of the drug, and if they occur within a few moments of its administration the drug must be exonerated. Diarrhea is occasionally seen as a sign of digitalis intoxication. An unusual symptom, but one which occasionally precedes the others, is dimness of vision, or yellow vision (Sprague, White and Kellogg).

Although the gastric disturbances are the most obvious and uncomfortable results of excessive digitalis dosage, the most dangerous results have to do with the effect on the functions of the heart itself. These effects may occur in patients with acutely diseased hearts (such as rheumatic carditis) after a much smaller dose than is required in other types of patients (Swift). Digitalis may cause such an increase in the conduction time from auricle to ventricle as to lead successively to an increased auriculo-ventricular interval in the electrocardiogram, to dropped beats, and to complete heart-block with independent auricular and ventricular rhythms and a ventricular rate usually less than thirty-five. The increased irritability produced by digitalis may lead to the formation of ectopic impulses. This effect may be limited to the production of occasional premature beats, usually ventricular in origin, or may progress to the stage of bigeminy, in which the heart-beats occur in pairs, each normal beat being followed by a premature one. This relation of coupled normal and premature beats is most commonly seen when large doses of digitalis are administered to patients with fibrillating auricles, and is a common and useful sign of intoxication. Premature beats observed before digitalis has been given do not constitute a contra-indication to its use; such premature beats often disappear during the period of digitalis action (Otto and Gold). If the intoxication be continued, however, series of ectopic impulses may be formed and dangerous ventricular tachycardia may be set up. Fibrillation of the auricles may occasionally develop during digitalis administration, particularly when the heart is the seat of severe disease (Resnik). A marked phasic variation in the rate of the heart, not related to respiration, is sometimes seen. Other irregularities of the heart-beat may be seen by electrocardiographic study to be due to so-called "ventricular escape." The sequence of toxic rhythms in man is not very different from that observed experimentally in the cat (Luten, 2). The cessation of administration of digitalis should be ordered, then, if anorexia, nausea, vomiting, diarrhea, or visual disturbances occur. The drug should also be discontinued if the heart rate falls much below sixty, if a sudden halving of the rate appears, if a previously regular rhythm becomes markedly irregular, if coupled beats appear, if marked variations in rate occur at intervals of a few seconds, and in the event of the sudden development of tachycardia.

CONTRA-INDICATIONS TO THE USE OF DIGITALIS

When a partial heart-block is already present, or in the presence of the rare ventricular tachycardia, digitalis if used at all, should be administered with great caution. In complete heart-block associated with heart failure digitalis may diminish the symptoms of failure without effect on the block and should be given, but not too rapidly. In partial heart-block, the development of which has coincided with the development of congestive failure, digitalis may be administered but only with caution. Under these circumstances one occasionally sees after digitalis therapy an improvement in the symptoms of failure accompanied by improvement in the conduction ability of the junctional tissue. If the block increases to an injurious extent after digitalis it may be combated by atropin, since a considerable portion of the action of digitalis upon the junctional tissues is exerted through the vagi.

One of the important contra-indications to the administration of digitalis, particularly in large doses, is the possibility that the patient has already received the drug. Digitalis is slowly excreted and may remain in the body in effective amounts for many days. Under these circumstances the administration of what is presumably a safe dose may lead to dangerous toxic effects. The question of the previous administration of digitalis can sometimes be settled by the history. If not, then the toxic effects already enumerated are to be sought for. The electrocardiogram may show changes suggesting previous digitalis administration such as increase in the P-R interval or changes in the height or direction of the T-waves.

In acute infections involving the heart and in severe intoxication in general, the toxic effects of digitalis are apt to occur with smaller doses than under ordinary circumstances (Swift). The drug should therefore be given with additional caution to patients with such conditions. Certain effects of diphtheria on the heart resemble those produced by digitalis intoxication, and for this reason it has been suggested that diphtheria contra-indicates digitalis (McCulloch). Probably a better reason for not giving the drug is that the circulatory collapse of diphtheria is not the kind usually improved by digitalis. Recent evidence (Gold) suggests that in animals the tolerance for digitalis is not diminished by experimental diphtheria. The question cannot be considered as settled, but it is probably wise not to give digitalis in the absence of the specific indications already mentioned.

Recently it has been shown that digitalis acts harmfully upon the circulatory mechanism in animals suffering from surgical shock (Blalock, 2). It is probable, therefore, that in this type of circulatory collapse digitalis should be avoided. Formerly either high blood-pressure or aortic regurgitation was regarded as a sufficient contra-indication to the use of the drug.

It is now recognized that neither condition should be so regarded and it is known that in the presence of congestive failure the blood-pressure often falls after digitalis therapy (Meyer and Mullen).

The administration of digitalis is often advised in certain special conditions, particularly in pneumonia and as a preparation for surgical operation, and this usage requires discussion. In pneumonia digitalis has at least many of the same effects as when this disease is not present (Cohn and Jamieson, Levy). It is given with the object of preventing, if possible, the onset of cardiac failure. It is well recognized that pneumonia may precede the development of either of two types of circulatory failure, congestive heart failure, or circulatory collapse associated with low blood-pressure but not with edema. The latter is the more frequent. Cardiac failure with congestion may well have as an exciting cause the prolonged cardiac overwork which is associated with pneumonia (Harrison and Blalock). In patients who seem predisposed to this condition because of existing cardiac disease or previous history of heart failure, digitalis should be administered in effective amounts. In other people, however, the chief danger is not cardiac failure of the congestive type but circulatory collapse, and there is no conclusive evidence that the occurrence of circulatory collapse is prevented by previous digitalization. To these patients digitalis is not certainly beneficial and occasionally it may be injurious. If congestive failure should develop, digitalis can, by application of our recent knowledge, be given with such rapidity that a good effect can be secured within a few hours (Robinson). The question of the advisability of the routine administration of digitalis to patients with pneumonia cannot be considered as settled. If it is given to such patients the dose should be less than maximal, and the administration should be begun early in the disease.

Certain experienced observers have recently emphasized their belief that digitalis is apt to be harmful to patients with severe thyrotoxicosis and it is possible that in very severe cases of this type the administration of the drug may further intoxicate the patient (Plummer). However, digitalis is very useful in thyroid disease when, as is often the case, auricular fibrillation and congestive heart failure are present. It should be given more slowly, but there seems to be no valid reason for giving up entirely its therapeutic aid in thyrotoxicosis.

It is the custom in many places to give digitalis preoperatively to large groups of patients, particularly to those of middle or advanced age. This is done with two objects in view: one to prevent the development of congestive failure, the other to prevent the onset of surgical shock. It is quite true that by diminishing the increase in cardiac work produced by certain anesthetics (Blalock), digitalis may protect against the development of cardiac failure following operation. Patients who are apt to develop this complication are usually recognized as such and digitalis should be admin-

istered to them. That the administration of digitalis has any effect in preventing the onset of surgical shock, on the other hand, has not been demonstrated and evidence is available which suggests strongly that previous digitalization might be an unfavorable factor in the presence of surgical shock (Blalock; Marvin, Pastor, and Carmichael). For these reasons and because digitalis is such a toxic drug that it should not be given promiscuously, it is advised that only patients with obvious heart disease or with a history of failure should receive digitalis before operation.

In recent years the diagnosis of coronary occlusion has been made with increasing confidence and frequency. In this condition circulatory failure is usually of the type marked rather by weakness and hypotension than by edema. Digitalis is probably best avoided, although no clear evidence bearing on this point is available.

Angina pectoris is seldom manifestly improved by digitalis. Occasionally a case is seen in which improvement is apparently related to the administration of the drug. It may be tried, cautiously and not too hopefully.

In paroxysmal tachycardia digitalis is probably of no value as far as abolishing the tachycardia is concerned, but it should be given in the event of the appearance of symptoms of failure.

In general then, digitalis should be given only to those patients who already suffer from one of the primary indications for its use or when there exists evidence which suggests that these indications may develop. It should not be used too generously in anticipation of possible failure because if congestive heart failure develops an effective concentration of digitalis can be reached within a few hours.

PREPARATIONS AND ADMINISTRATION

An enormous variety of preparations of digitalis is available. For ordinary administration, however, nothing is superior to pills or capsules of the dried leaf if the strength of the preparation is known. A reliable tincture is almost equally satisfactory but has the drawback that in unskilled hands the doses are often inaccurately measured. If the tincture is used doses should never be measured by drops, which may run two or more to the minim, but always by a measuring glass. Reputable pharmaceutical houses now are able to say definitely that a given lot of digitalis leaves is of a given strength, because they are required to test each lot by observing its effect upon the hearts of animals, usually frogs or cats. Even so, it is desirable to test the efficacy of a new preparation for one's self by observing its effect upon the ventricular rate of a patient suffering with auricular fibrillation. If both animal experimentation and clinical observation agree that a preparation is potent it may be accepted. If a potent drug is used and a sufficient dose is given, the expected digitalis

effects will be obtained in most patients. Since, however, the effective dose is so near the toxic dose, it is desirable to have a means of determining approximately the amount which each patient will require for a full therapeutic effect. This is best done by calculating the dose in relation to the body weight of the patient (Eggleston). In general it may be said that if the total amount is administered within twenty-four or forty-eight hours about 1.5 grams of the leaf or 15 c.c. of the tincture will be required for each 100 pounds (45.5 kilograms) of body weight, exclusive of edema. Thus a man weighing 150 pounds will require about 2.25 grams of the leaf, or 2.5 c.c. of the tincture. This is true only if the preparation is accurately standardized so that 0.1 gram of the leaf (or 1.0 c.c. of the tincture) contains one cat unit. This dosage is safe only for patients who are in bed and under almost constant observation. For patients who are seen only once or twice a day it will be found more satisfactory to allow 1 gram of the leaves or 10.0 c.c. of the tincture per 100 pounds of body weight. Individual susceptibility may make a smaller dose effective or a larger one necessary. Children over four years old often not only tolerate but require considerably larger doses per pound of body weight than do adults. It is usually safe to allow half again as much (McCulloch and Rupe).

The total calculated dose should never be administered inside of twenty-four hours. In ordinary cases two to four days should be taken to attain maximum digitalization since toxic symptoms may appear at an unexpectedly early level and there is often a possibility that digitalis has been administered previously. If speed is necessary one-third of the maximum calculated dose may be given at once and followed in six hours by an additional one-sixth of the calculated total dose. This will usually produce a definite digitalis effect. The remainder of the calculated amount should be given in broken doses over the next thirty-six hours and symptoms of intoxication should be scrupulously watched for. Such rapid administration should not be undertaken in ambulant patients or in patients who cannot be frequently observed. These and less urgent cases may be treated by the administration of 0.2 gram three times daily, which will ordinarily have a recognizable effect in twenty-four hours and a maximum effect in three to four days. This is a satisfactory method for routine use and is rapid enough for the majority of cases. If three or four days are taken for the administration of the calculated dose a slightly larger amount must be given to allow for the excretion of the drug.

After a therapeutic response has been observed or the calculated dose has been administered the concentration of digitalis in the body may be maintained by the daily administration of 0.1 to 0.2 gram. The administration of 0.1 gram and 0.2 gram on alternate days will supply a weekly total of approximately a gram and maintain most patients at a nearly even level. The rate of the excretion varies somewhat in different people and

must be established by individual observation in each case. The rate also varies with the amount of the drug in the body, that is, the patient does not eliminate a fixed quantity of digitalis per day but a percentage of that which is in the body at the time (Gold and DeGraff).

When the attempt is made to abolish flutter of the auricles by the administration of digitalis the drug may be given up to the point where the flutter changes to fibrillation unless toxic manifestations appear first. The drug should then be withdrawn and in a fair proportion of cases the rhythm will revert to normal within a few days.

In vomiting patients digitalis may be administered by rectum by the method recently described by Levy. The tincture may be used if sufficiently diluted but is somewhat irritating. An aqueous solution of strength equal to the tincture is prepared by some pharmaceutical houses and is convenient for rectal use. The dose should be the same as when given by mouth, but since frequent administration is not practical, individual doses will be larger and further apart. In the first dose one may give one half the amount calculated as necessary and twenty-four hours later a quarter of the total dose. Subsequent dosage and route will depend on the circumstances of the individual case. The technic used in the administration of digitalis by rectum is not difficult. The patient receives a preliminary cleansing enema. After evacuation a rectal tube of small caliber is inserted about 15 centimeters into the rectum. Through this the digitalis solution is given and washed through with tap water (25 c.c.). The funnel through which the digitalis is poured is held 30 to 40 centimeters above the level of the rectum. After the tap water has flowed in, the tube should be clamped, left in position for fifteen minutes and then slowly withdrawn. The patient should resist any desire for a bowel movement for at least six hours.

Where circumstances forbid the use of either the oral or rectal routes (for example, the simultaneous presence of both vomiting and diarrhea) or when the occasion is so urgent that even a few hours' delay is unsafe, a digitalis preparation may be given intravenously. If the intravenous administration of digitalis is contemplated, it is of the most urgent importance to know of any digitalis therapy within the preceding fortnight, because the sudden addition of even a small amount in the blood stream may provoke serious intoxication.

Of the many preparations for intravenous use the best and safest, because its strength is accurately known, is crystalline ouabain (Robinson, White, Eggleston and Hatcher). Only in the rarest instances should the attempt be made to accomplish full digitalization by the intravenous route. When an immediate effect is demanded one may give 0.5 milligram of crystalline ouabain intravenously, and at the same time begin the administration of digitalis by mouth or rectum. If neither oral nor rectal therapy is feasible, further intravenous injection may be made at intervals of six

hours. These subsequent doses should not be larger than 0.25 milligram, and toxic effects should be the signal for cessation of their administration. The amount of ouabain required for a full digitalis effect is not known, and it is therefore not safe to attempt to secure saturation by the intravenous route. A total dosage of 1 milligram is usually safe. As soon as possible, the intravenous route should be abandoned. If more digitalis is required it should be given by mouth or by rectum.

With the exception of the preparations for intravenous use the drugs related to digitalis (squill, strophanthus, apocynum and convallaria) have no advantages over digitalis leaf itself. They are poorly and irregularly absorbed, dosage and effect are alike uncertain, and the abandonment of their use would simplify treatment without detriment to the patient. So far as present knowledge goes, the effect of these drugs does not differ from that of digitalis itself. If future work shows that some useful effect, lacking in digitalis, is seen in the action of one of the allied drugs, a place in therapy will be made for it.

It should be said that the action of digitalis and the nature of the disturbances in which it is used are at present the subjects of thought and study in many places. It is probable that the next few years will see changes in the methods of using digitalis. In the present state of our knowledge, however, it is safest to limit its use to those cases in which the indications are clear.

In conclusion the point should be emphasized that digitalis, while one of the most important drugs used in the treatment of cardiac disease, does not in itself constitute adequate treatment in any case. Other drugs, such as sedatives and diuretics, are of nearly or quite equal importance, and the treatment by methods other than the administration of medicine is sometimes the most important of all.

No attempt is made in this chapter to refer to all of the many papers which have added to our knowledge of digitalis. Reference is made to a few of the recent publications which bear directly upon the questions under discussion. For most of the enormous literature the reader is referred to the comprehensive review by Robinson.

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CHAPTER XLIII

THE TREATMENT OF HEART DISEASE, PARTICULARLY HEART FAILURE, BY MEASURES OTHER THAN DIGITALIS

H. M. Marvin

General Considerations.—The present chapter is devoted to a consideration of the drugs other than digitalis which may properly be employed in the treatment of heart failure, and to a brief discussion of certain therapeutic measures that do not involve the use of drugs.

In considering the treatment of *congestive heart failure,* it is desirable to distinguish the earlier from the later stages. Early congestive failure is usually characterized by one dominant symptom, namely, breathlessness on exertion. There may be, in addition, slight edema of the feet and ankles in the afternoon or evening, and possibly a little orthopnea, but the patient is comfortable while at complete rest, and there is no evidence of venous engorgement. The only drug needed in this stage of failure is digitalis, which should be administered in full dosage and continued for some weeks; if it is then apparent that it is without effect upon the symptoms, it should be discontinued.

There are certain general considerations that should be kept clearly in mind in treating early congestive heart failure; they are often more important at this stage than the proper use of digitalis. It is clear that patients with even slight disability should not be permitted to remain, or to become, overweight, as additional weight inevitably necessitates additional work by the heart whenever physical exertion is undertaken. While it is unnecessary, therefore, to place particular emphasis upon the *type* of diet, it is important to regulate its caloric value in such a way that the body weight will not rise above the normal. Fluids may be allowed in sufficient quantities to quench thirst, but should not be forced; if there is even slight edema throughout the entire day, the total quantity of fluids should be restricted. Daily evacuation of the bowels should be ensured, by a mild cathartic if necessary. Insistence should be placed upon adequate hours of rest and sleep; not only should such patients retire at an early hour in the evening, but they should be required to rest for one or two hours after the noon meal whenever circumstances make this possible. Many individuals with early heart failure show an immediate and gratifying response to an occasional day of complete rest in bed; the

benefit derived from a week-end in bed once or twice a month is usually so apparent to the patient that it is not difficult to enforce the continuance of the practice. All patients with heart failure should be told of the danger of infectious diseases, especially those of the upper respiratory tract, and should be cautioned against exposing themselves to such infections when they are epidemic. If the tonsils are present and are the site of repeated infections, their removal should be advised at a time when infection is quiescent.

The more advanced stages of congestive heart failure are characterized by such manifestations as cyanosis, venous engorgement, dyspnea on slight exertion or even while at rest, orthopnea, cough, edema of the dependent portions of the body, and possibly fluid accumulations in the serous cavities. In the discussion that follows, it is assumed that digitalis has been given and that the patient is in bed, since these are the most important therapeutic measures in this condition; without rest and digitalis, other treatment is largely valueless. There are no other drugs which have the same general effect as those of the digitalis series, but there are others that may be given for the relief of one particular manifestation of heart failure. In general, they may be divided into those that are given to produce sleep (hypnotics), those given for the purpose of removing excess fluid (diuretics), those used for their effect upon the respiration, and those employed for their effect upon the cardiac mechanism. It is convenient to consider them in these four groups.

Hypnotics.—Hypnotics become necessary at some time in the treatment of almost every patient with heart failure. There is general agreement that adequate sleep is essential if there is to be any improvement, and hypnotics should, therefore, be used without hesitation when symptoms demand their exhibition. It is not often that physicians refuse hypnotics to restless patients, but too often it happens that the doses given are entirely inadequate; too often the physician is content with having prescribed the amount that is theoretically correct, even though the desired objective is not attained. The proper dose of any hypnotic is, of course, the amount that is necessary to cause sleep, whether it be much less or much more than the dose recommended by textbooks or manufacturers.

Morphin sulphate is unquestionably the hypnotic of greatest value, for not only does it bring sleep to the dyspneic patient, but it also often removes temporarily the great burden of mental suffering and anxiety which has intensified the physical discomfort. It is the drug of choice if a patient with congestive heart failure has had several sleepless nights, whether or not milder hypnotics have been tried. A dose of 0.016 gram (¼ grain), hypodermically, is usually sufficient for an adult, but whenever possible a second smaller dose should be made available for use later in the night if it should prove necessary. If other hypnotics have failed,

and morphin has become the only effective one, the usual increase of dosage may sometimes be avoided by combining with it a small amount of hyoscin hydrobromid, 0.00065 to 0.00043 gram (1/100 to 1/150 grain), although the action of the combination is not so happy in cardiac patients as it often proves to be in those with chronic nephritis.

Of the milder hypnotics *chloral hydrate* is probably the most satisfactory. It has many advantages over most hypnotic drugs in that it may be administered by mouth or by rectum, it is well tolerated by almost all patients, it is effective in most, the sleep that it induces is very similar to the normal, and it often exerts the same hypnotic effect, even though administered frequently over a long period of time. It may be given alone in solution, or in the form of the well-known chloral-bromid solution, which is usually so prepared that the amount of bromid is slightly larger than that of the chloral. The usual effective dose of chloral for an adult is 1 to 1.3 gram (15 to 20 grains) if given by mouth; slightly larger doses may be given per rectum, and amounts as large as 1.6 to 2 grams (25 to 30 grains) may safely be used if smaller doses prove ineffective. The present writer has never encountered an instance in which intolerance to the drug or undesirable side-actions have been manifested, nor has he ever observed any evidence of the often-mentioned "depressing" effect of chloral upon the circulation.

Codein sulphate, administered by mouth or hypodermically, is usually not effective as a sedative unless the chief cause of wakefulness is cough. In combination with some of the barbital derivatives, it is often highly satisfactory. Doses of less than 0.030 gram (½ grain) are usually without significant action in an adult, and amounts twice as great often give satisfactory results when smaller doses have failed.

Luminal by mouth, or luminal sodium by hypodermic injection, has proved useful in only a very small proportion of those cardiac patients to whom it has been given by the writer. Not only does it often fail to produce the desired sleep, but in many instances it also appears to cause nausea or to aggravate nausea already present. Doses of 0.030 to 0.090 gram (½ to 1½ grains) of luminal may be tried, either alone or in combination with 0.030 gram (½ grain) of codein sulphate.

Barbital (veronal) is usually of little value in those patients whose sleeplessness constitutes a therapeutic problem. The dose is 0.3 to 0.6 gram (5 to 10 grains), by mouth, preferably in warm milk. Like luminal, it appears to be much more effective if combined with codein.

Paraldehyd in doses of 4 to 16 c.c. is a very effective hypnotic in most cases, but there are few patients who will voluntarily continue its use because of the taste and the odor during its excretion.

Of the more recent proprietary preparations, adalin and allonal have proved the most satisfactory in the writer's experience. A few patients

with advanced heart failure have been observed in whom morphia induced excitement, and who responded most satisfactorily to adalin or allonal. The usual dose of the former is 0.3 to 0.6 gram (5 to 10 grains); of the latter, 0.160 to 0.320 gram (2½ to 5 grains). As in the case of the other mild hypnotics, these may be combined with codein if desired.

Diuretics.—Diuretic drugs are indicated whenever a patient has subcutaneous edema, hydrothorax, or ascites, after rest and digitalis have been properly employed. Numerous drugs are available; few of them are of proven value. The most important are the xanthin derivatives, theophyllin (theocin) and theobromin, and the mercurial preparations, novasurol and salyrgan. Of the xanthin diuretics, theocin is the most powerful; it often causes great diuresis, raising the urinary volume from a daily average of a few hundred cubic centimeters to 6 or 8 liters in twenty-four hours, with corresponding reduction in body weight and in demonstrable edema.[1] In effective dosage, theocin is seldom tolerated for more than two or three days, and often causes nausea and vomiting after one or two doses. Its therapeutic usefulness is greatly limited by this undesirable side-action. Theocin-sodium acetate and euphyllin (theophyllin ethylenediamin) have been recommended as possessing the diuretic potency of theocin without its nausea-provoking properties, but if comparable doses are used, nausea seems to occur as quickly with one as with another. The dose of theocin is 0.2 or 0.3 gram (3 or 5 grains) given three times daily for two or three consecutive days, and repeated at intervals of not less than five days. Even if theocin causes great diuresis when first used, it is apt to prove much less effective at subsequent exhibitions, and not infrequently patients lose all response to it after a few trials. If the first and second attempts fail to cause diuresis, it is very seldom, indeed, that success will attend any subsequent ones.

Theobromin often causes satisfactory diuresis, and seldom provokes nausea, but it is a less potent drug than theocin. Theocin will often prove highly effective after theobromin has failed; the reverse is not true. The dose of theobromin is 0.6 gram (10 grains) thrice daily for two or three days; it is administered in gelatin capsules.

Theobromin sodiosalicylate, or diuretin, has proved the least potent of the xanthin diuretics in the experience of the writer, although it is the one most frequently employed by the practitioner. Even in doses as large as 4 or 5 grams (60 to 75 grains) daily for five or six days, it is often devoid of significant diuretic action. That it is not actually valueless is shown by a recent case in which there was an excellent diuretic response to this preparation after theocin and theobromin had failed completely.

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[1] It is to be noted that frequent determinations of the body weight constitute the best method of ascertaining decrease in edema; it should also be kept in mind that the loss of weight is usually greater than would be expected from the measurement of fluid intake and urinary volume.

If theobromin sodiosalicylate is used, it should be given in doses of 4 to 5 grams (60 to 75 grains) per day.

A more recent preparation, *theocalcin* (theobromin calcium salicylate), is theoretically more acceptable than any of the other xanthin combinations, since it is the only one which combines two diuretic substances. While the available reports of its action are not very numerous, they are such as to indicate that it is about as potent a diuretic as theocin, and is tolerated much better by the patient. The present writer has employed it but little, but it has proved most satisfactory in every instance. The daily dose is 3 to 5 grams (45 to 75 grains) for two or three days.

Caffein is often grouped with the xanthin diuretics; actually, it should not be regarded as a diuretic, since its relatively feeble action in this respect is completely overshadowed by its effect upon the higher cerebral centers and the respiration.

Novasurol, a mercurial preparation originally introduced for the treatment of syphilis, can probably be regarded as the most potent diuretic now available. It is marketed in sterile ampuls, and may be administered by intramuscular or intravenous injection; the latter is the method of choice, since an occasional intramuscular injection results in tissue necrosis at the site of injection. It is customary to administer a small dose (0.5 c.c.) as a preliminary measure, in order to be sure that there will be no unfavorable reaction; if there is none, the full dose of 2 c.c. may be given one or two days later. The diuresis begins within several hours and has largely ceased within twenty-four hours except when an acid-producing salt has been given earlier. The drug usually produces the most extraordinary diuresis, with urinary volumes of 9 to 11 liters in twenty-four hours, and a corresponding loss of 15 to 20 or more pounds in body weight. Such diuresis not infrequently occurs in patients who show no response whatever to theocin. Thanks largely to the work of Keith and his collaborators, it is now known that the administration of ammonium chlorid (6 to 10 grams per day) or of ammonium nitrate (10 to 12 grams per day) for a few days preceding the novasurol, results in much more intense diuresis for a longer period; in such circumstances, it is not unusual for a patient to have a fluid output of eight or nine liters both on the day of the novasurol injection and on the day following. Ammonium nitrate is tolerated better than ammonium chlorid.

Undesirable effects from novasurol have undoubtedly been witnessed, but they are not sufficiently numerous or severe to weigh heavily against the use of the preparation. Salivation and stomatitis, if they occur, are usually not troublesome; mercurial colitis occurs so infrequently that it cannot be regarded as a contra-indication. Clinical evidence of renal damage is yet lacking, but microscopic study (in this clinic) of the kidneys from patients dying shortly after receiving novasurol have revealed in several instances typical mercurial injury of the tubal epithelium. In the

opinion of the writer, the possibility of any one of these effects is not sufficient to justify the withholding of novasurol. If a patient has reached the stage of heart failure when he is waterlogged even after rest, digitalis, and the xanthin diuretics, the physician is confronted with a choice of allowing him to die in great discomfort without novasurol, or of administering it in the hope that it may prove effective. Happily, it does so in most cases.

Novasurol may be repeated at intervals of four to seven days; more frequent administration is practiced by some, but is probably undesirable. It should not be given if the patient is greatly emaciated or has high fever, and it is the belief of most observers that it should not be used if there is evidence of renal damage, although it has actually been used in the treatment of chronic nephritis with edema. It has to be kept in mind that patients with advanced congestive heart failure uniformly show albumin, cells, and casts in the urine, that the excretion of phenolsulphonephthalein is usually lowered, and that the non-protein nitrogen of the blood is often moderately elevated; it is, therefore, very difficult in some instances to decide whether the findings indicate merely renal congestion or actual renal damage.

Calcium salts, although useful in the treatment of edema due to nephritis or diabetes, have little diuretic action in patients suffering from heart failure. Clinical studies indicate that calcium chlorid occasionally causes moderate diuresis in cardiac patients, but they fail to lead to the conviction that it is of any importance as compared with the xanthin diuretics or with novasurol.

Urea is probably of little or no value in ridding the edematous patient of his excess fluid, but it occupies a definite place in the treatment of those who have lost their edema through other measures, and who gradually or rapidly reaccumulate it if left untreated. It is one of the few drugs that can be given daily for indefinite periods; it often maintains the fluid excretion at a high level relative to the fluid intake, thereby slowing the rate at which the edema returns, or even preventing its return for many weeks. It is usually administered in the form of a 20 per cent solution, as cold as possible because of its unpleasant taste; 40 to 60 grams daily are necessary for effects. After urea has been administered for several days, the blood non-protein nitrogen should be determined, in order to be sure that the substance is being readily excreted. If it is not properly excreted by the kidneys, there will be no diuretic effect, the level of the non-protein nitrogen in the blood will rise rapidly, and urea must be discontinued.

Recent reports in the German literature appear to indicate that bismuth, injected intramuscularly, is a valuable diuretic drug, sometimes causing conspicuous diuresis after theocin and novasurol have failed. The number of such reports is still too small to permit any final statement

as to the value of bismuth, but some of the recorded cases are sufficiently convincing to justify the use of this drug if other diuretics have been tried without success.

Drugs Acting on the Respiration.—Of the drugs used for stimulation of the respiration, only one is of undoubted value: *caffein*. It is most effective when given by hypodermic injection in the form of caffein sodium benzoate. There is considerable evidence to indicate that it has an action upon the heart also, but its chief effect is manifested in the quickening and deepening of the respirations. In addition to this objective change, there is usually also subjective relief; the patient often comments that his breathing is easier. Doses of 1 gram (15 grains) of the combination, containing equal quantities of caffein and of sodium benzoate, may safely be given subcutaneously, or even intravenously; larger doses have actually been administered directly into the blood stream, but should probably be reserved for subcutaneous injection. Doses of half the size mentioned are distinctly beneficial in some cases. Caffein has to be repeated at intervals of several hours in most cases, as its effect is rather transient. The chief objection to its use is that it renders the patient wakeful and alert and usually prevents satisfactory sleep.

Drugs Acting on the Heart.—Before considering the drugs that are used for their specific effect upon the cardiac mechanism, it is desirable to mention briefly several substances that are often employed for their supposed stimulating action upon the heart. Cactus and cactin, marketed in the form of the widely advertised cactina pillets, have been conclusively shown to be completely inert: there is not the slightest scientific foundation for the claims advanced for this preparation, nor the faintest justification for its use in cardiac patients. Strychnin likewise has failed to support the enthusiasm once manifested for it, and there is abundant evidence to-day to indicate that it cannot allay or remove symptoms due to myocardial insufficiency. It is possible that it may have had some action in those few patients who have received the drug directly in the myocardium after apparent cessation of the heart's action, but as customarily used in patients with heart failure it is valueless.

Cardiazol (pentamethyltetrazol), one of the most recent preparations to be heralded as a valuable drug for use in heart failure, also appears to have little action that would justify the claims made in its behalf. The numerous indications for its use, and the wide diversity of the conditions which it is supposed to benefit, are in themselves sufficient to cast doubt upon its value; and many of the reports in the German periodicals are notable for their lack of suitable control observations. Barker and Levine have recently studied the action of this substance in experimental animals, and have reached the following conclusion: "In a series of experiments on cats, it was found that cardiazol did not have any beneficial effect on the cardiorespiratory mechanism. This was true in the normal

animal and in states of depression produced by quinidin, hemorrhage, and acid intoxication." Further experience is needed before any final comment can be made, but at the moment it seems very doubtful if cardiazol will be a permanent addition to the list of drugs available for the failing heart.

Coramin-Ciba (pyridin-B-carboxylethylamid) is another preparation that has been highly extolled in the German medical press during the past several years. The claims made for it are even more astonishing than those advanced for cardiazol; by various writers it is stated to be of value in pernicious anemia, in chronic gall-bladder disease, in pneumonia, in bronchitis, in conditions of collapse from any cause, and in all circulatory diseases. It is said to be an excellent stimulant for pre- and postoperative use, and for all types of poisoning; it even improves the appetite of infants and children! It goes without saying that there is no acceptable evidence advanced in support of these diverse claims, and in the present state of our knowledge there appears to be no justification for the employment of coramin except as a purely experimental measure. By most writers, the action of coramin is said to be very similar to that of camphor; since camphor is now generally believed to be without significant effect upon the circulation, the statement is equivalent to saying that coramin is devoid of action.

Camphor, long regarded as the stimulant par excellence, as the one final measure to be employed when all others had failed, is apparently devoid of all action upon the heart when used in therapeutic doses or even in doses many times greater than those customarily employed. Its action has been repeatedly tested upon the circulation of experimental animals and of human beings with normal and with diseased hearts. No evidence has yet been obtained to indicate that it is of the least therapeutic value.

Quinidin.—Of the drugs employed for their specific effect upon the cardiac mechanism, quinidin is the most important. Few drugs used in the treatment of heart failure have received such extensive and favorable comment as did quinidin in the several years following the publications of von Frey, although the earlier statement of Wenckebach that quinin would bring auricular fibrillation to an end attracted little attention. Hailed at first as a specific treatment for auricular fibrillation, it has required some years for sufficient observations to accumulate to afford a basis for rational judgment of the value of quinidin. At the present time, opinion seems to be fairly uniform as to the indications for its use, and as to the results that may be expected.

Thanks largely to the work of Lewis and his associates in England, and of Levy in this country, the precise effect of the drug upon the cardiac tissues is quite clearly understood. For a detailed discussion of its action the reader must be referred to the original papers of these workers. It is perhaps sufficient to mention at this point that quinidin exerts a dual

effect upon the auricular muscle. It slows the rate of conduction of the circulating excitation wave which is responsible for auricular fibrillation and auricular flutter, and at the same time it lengthens the refractory period following the passage of the excitation wave. Now these two effects are directly opposed, so far as their relation to the mechanism of auricular fibrillation is concerned: the decrease in the rate of conduction tends to make auricular fibrillation more permanent, while the lengthening of the refractory period tends to bring the circus movement to an end and thereby restore normal mechanism. It is only when the latter effect exceeds the former in a given case that normal mechanism is resumed; the actual number in which restoration to normal mechanism occurs varies from 50 to 75 per cent in different clinics.

In the present state of our knowledge, the drug should probably be used for the following purposes: To restore the normal rhythm in a certain group of patients with auricular fibrillation; to convert auricular flutter to normal mechanism if the usual method of treatment with digitalis alone has failed; to lessen the frequency of paroxysms of tachycardia, or prevent them altogether; to lessen the frequency of premature beats when they are very troublesome; and, finally, to arrest paroxysms of tachycardia that have resisted the usual methods of treatment. A few words may be said about each of these conditions.

It is generally agreed that restoration of normal mechanism should not be attempted in those patients with auricular fibrillation who have congestive heart failure at the time, or who have had it in the past, nor in those who have had at any time embolic accidents which might reasonably be regarded as indicating the presence of thrombi in the auricles. The reason for withholding quinidin from those who have, or have had, heart failure, is that clinical experience has demonstrated that the normal rhythm, if resumed, seldom persists for more than several days or weeks, and that there is little or no improvement after normal mechanism has been restored. Refusal to administer the drug to patients who presumably have thrombi in the auricles is based upon the likelihood of the restored auricular contractions breaking off fragments and causing fatal embolism. Such accidents have been witnessed, but the actual percentage of embolic phenomena following the restoration of normal rhythm by quinidin appears to be less than that observed in untreated auricular fibrillation.

The use of the drug for the purpose of restoring normal mechanism is reserved, then, for those whose fibrillation is of recent origin, who have not had heart failure, and who have had no evidence of embolism. This means, practically, that it is reserved for young people with rheumatic heart disease (although there are notable exceptions), and in such patients it is often of considerable value. The duration of the normal rhythm that follows the use of quinidin is often a matter of many months, or even several years, but in the experience of the author the fibrillation eventually

returns, the intervals between treatment with quinidin become steadily shorter, until finally the drug is no longer effective and digitalis has to be substituted.

Quinidin is usually administered in the form of the sulphate, in gelatin capsules containing 0.2 gram (3 grains) each. It is customary in beginning treatment to give 0.2 gram twice, separated by an interval of two or three hours, in order to determine whether the patient has an idiosyncrasy to the drug. It is not uncommon to have the patient mention palpitation shortly after receiving the test dose, as the ventricular rate is usually elevated moderately by such quantities; other symptoms are exceedingly rare. On the following day, full dosage may be employed, and this usually consists of 0.4 gram (6 grains) administered from three to six times a day, five times being the customary number in many clinics. In very young subjects, this dose may be reduced to three times per day; in resistant patients, it is often given in amounts of 0.6 or 0.8 gram (9 or 12 grains) four or five times a day. These large doses are seldom effective in restoring normal mechanism if the smaller ones have been tried without success. It is necessary to continue the treatment for a week or ten days before deciding that the drug is ineffective. During the course of treatment, transient and unimportant toxic symptoms may develop, such as headache, tinnitus, nausea, vertigo, disturbed vision, and palpitation; these usually disappear promptly when the medication is discontinued.

Quinidin appears to be more effective in restoring normal mechanism if digitalis has been given previously, despite the fact that the two drugs exert directly opposite effects upon the mechanism responsible for auricular fibrillation. It is the author's firm belief that all patients who are to receive quinidin should be completely digitalized first. The effect of continuing quinidin medication after restoration of normal rhythm cannot be said to have been determined satisfactorily, but many patients are known to have relapsed into auricular fibrillation while taking such "rations" of quinidin, and it is probable that most patients do as well without them.

In the treatment of auricular flutter, quinidin seems to be a logical supplement to digitalis in the event that the latter fails to effect the restoration to normal rhythm. In a recent review of a large series of flutter cases, Parkinson and Bedford found that as between digitalis alone and quinidin alone, digitalis was much the more valuable drug. But occasionally digitalis converts auricular flutter into auricular fibrillation, and the further step to normal mechanism does not follow; in such cases, quinidin will often complete the restoration, and should be used in the doses mentioned above.

Quinidin is of proven value in the prevention of paroxysms of tachycardia. In many patients, very small doses, such as 0.2 gram (3 grains), taken once or twice every second day, will suffice to prevent the tachycardia

for almost indefinite periods. That such small doses are actually effective may be shown in these same individuals by having them discontinue the drug altogether, when the paroxysms reappear. Others are obliged to take the drug several times daily, and there is no evidence that daily doses over periods of many months are harmful.

It is seldom necessary to resort to quinidin in the treatment of a paroxysm of tachycardia, but it has more than once been of service during such seizures. If the customary methods of vagal stimulation have proved ineffective after repeated trial, quinidin sulphate may be given in doses of 0.4 gram (6 grains), five or six times a day, at two-hour intervals; the author has observed three paroxysms apparently stopped by such treatment. In each instance, the rate slowed gradually over a period of hours, instead of stopping abruptly; suggesting that the cessation of the tachycardia was actually due to the quinidin and was not a mere coincidence.

Premature beats are not often sufficiently disturbing to require specific treatment. Their presence in a patient whose heart is otherwise normal should lead to a search for infective foci; if none is found, quinidin may be given in small daily doses. It usually has to be continued for weeks or months; occasionally the premature beats seem to disappear permanently after several months of quinidin therapy.

For the prevention of the convulsive (Stokes-Adams') seizures of complete A-V heart-block, adrenalin has been used and has apparently been of value in many cases. It is not without danger, however, as it sometimes provokes the very seizures that it is employed to prevent. Cohn and Levine have pointed out that barium chlorid,[2] presumably because of its irritant effect upon the ventricle, often prevents the Stokes-Adams' attacks for considerable periods of time; available reports seem to indicate that it is effective in 50 to 60 per cent of the patients with convulsive seizures. The dose recommended is 0.030 gram (½ grain), four times a day. Thyroid extract, in doses of 0.2 to 0.65 gram (3 to 10 grains) daily, has been reported as effective after barium had failed, and ephedrin is also of value in occasional cases. The latter drug is given by mouth in doses of 0.020 to 0.030 gram three times a day.

GENERAL THERAPEUTIC MEASURES

Diet.—The general indications for the diet of a patient with congestive heart failure are that it should not contain large amounts of fluid or of salts, and that it should be relatively high in caloric value without too much residue. In the earlier stages of failure, when there is but moderate breathlessness and little edema, a normal mixed diet is usually well taken, and no particular restrictions are indicated. In the later stages, and

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[2] See article tby Hermann in this volume.

especially when there are symptoms due to engorgement of the abdominal viscera, diets with a large residue should be avoided, and the total amount of fluid should be restricted to 1.200 or 1,500 c.c. per day. The Karrell diet, consisting of 800 c.c. of milk per day, with no other food or fluid, has long been popular as a temporary measure. As it is not a maintenance diet, it cannot be continued for more than several days, but it is often of considerable value in beginning the treatment of a patient who has large amounts of edema. A specific diet for patients suffering from heart failure has been recommended by Smith and his collaborators; a diet based upon the belief that the heart often fails because it does not receive sufficient food for energy. The diet contains approximately 2,100 calories, and is made up of 44 grams of protein, 110 grams of fat, and 222 grams of carbohydrate, with a minimal amount of salt and not more than 1,500 c.c. of fluid. The following excerpt from their paper indicates the character of the diet: "It is served in the form of milk, cream, butter, eggs, vegetable purees, cooked cereals and fruit juices. The carbohydrate is further increased by the addition of sugars, as dextrin maltose, dextrose and lactose. Small and frequent feedings are given to avoid gastric retention and fermentation. When edema is present, the liquid intake is limited to 1,500 c.c. and the salt is reduced to a minimum. Usually on the third or fourth day other foods, as jelly, crackers (salt-free), toast, and stick candy, are added. Later, about the eighth day, depending upon the condition of the patient, pureed fruits and additional pureed vegetables are incorporated. Gradually the consistency of the food is changed from that of the soft to that of the light diet." The results reported from the use of this type of diet in more than fifty cases would seem to justify its widespread adoption.

Venesection.—Venesection, after holding a preëminent place among therapeutic procedures for centuries, in recent decades fell into complete disuse. In the past few years, its place in the treatment of heart failure is again being discussed, and several observers have made a plea for its occasional and judicious employment. Unquestionably one of the reasons why bleeding has not gained greater favor in recent years is that the evidence brought forward in its behalf completely fails to stand the test of critical survey. There is but one logical indication for venesection in a patient with congestive heart failure, namely, increased venous pressure. In some cases, the removal of 500 c.c. of blood from a vein in the arm results in a prompt reduction of venous pressure to normal. In a small percentage of such cases the pressure remains normal; in a larger percentage, the venous pressure again rises, and may again fall to normal after a second venesection. It is clear that the procedure cannot be employed frequently. The recent work of Eyster and Middleton suffices to show the beneficial effect of bleeding upon the venous pressure, but it does not indicate that the measure is of great importance in prolonging life.

Removal of Fluid Accumulations.—Most patients with heart failure who have considerable edema will present at some time evidence of transudates in the pleural or peritoneal cavities, and these are often of sufficient size to interfere seriously with respiration. If there is prompt response to rest, digitalis, and diuretics, the mechanical removal of this fluid will be unnecessary, but if it remains after the above measures have been tried, it should be removed through a trocar introduced after local anesthetization. The operation is painless if properly performed. Amounts of fluid as great as 1,200 to 1,800 c.c. may sometimes be removed from one pleural cavity, but often the patient becomes cyanotic and begins to cough before the entire quantity is removed, and in such cases it is wiser to withdraw the trocar and perform a second paracentesis on a later day. In the case of ascites, it is wise to remove the entire amount present if possible.

Cathartics.—The author is not one of those who hold that saline catharsis is a valuable method of removing edema fluid. If there is considerable edema, there is fairly advanced heart failure, and it seems wholly illogical to subject patients with heart failure to the exertion entailed by frequent bowel movements, especially if the bed pan has to be used. The amount of fluid that can safely be removed through the bowel by catharsis is inconsiderable, and the same end can be attained with greater safety and far greater comfort to the patient by the judicious use of the diuretics mentioned earlier. Cathartics should be used for the purpose of securing satisfactory evacuations of the bowel, and for that purpose alone. It is the firm belief of the author that most cardiac patients should be allowed to use a commode at the bedside rather than the bed pan; the exertion incidental to stepping to the floor and sitting comfortably upon the commode is almost always less than that necessary to support the body in the strained position assumed by most patients when using the bed pan. In the last stages of failure, it is, of course, impossible to consider the use of the commode.

Glucose.—Evidence is steadily accumulating to indicate that the intravenous injection of glucose solutions is often of great value in the treatment of congestive heart failure. There is no complete agreement at the moment concerning the mechanism of its action; by various observers it has been stated that glucose acts as a source of readily utilizable energy, that it replenishes the glycogen stores of the heart, that it causes a dilatation of arterioles and capillaries, thereby lowering high blood-pressure, and that it alters the osmotic relations of the body fluids in such a manner as to make the circulation more efficient, and often cause great diuresis. It has been shown that the injection of glucose causes certain definite and unmistakable changes in the human electrocardiogram, such as prolongation of the A-V conduction time, slight changes in the R wave, the appearance of Q and S waves if they were previously absent, and a shift in the

position of the T wave. Changes in the respiration have also been observed. In experimental animals poisoned with diphtheria toxin, glucose solutions have been found to be the most effective agent in raising the blood-pressure after it had fallen to very low levels. Clinically, the intravenous administration of the sugar has been noted to result in prompt and conspicuous improvement in the condition of the patient. The amount recommended by most authors is 200 to 250 c.c. of a 10, 15, or 20 per cent solution, given two or three times a week. The same end may be more easily attained by using smaller quantities of a more concentrated solution; adults may safely be given 50 to 100 c.c. of a 50 per cent solution. This solution is marketed in sterile ampuls, each containing 50 c.c., and the contents may be injected with a syringe, making unnecessary the more complicated apparatus required for the larger quantities. The solution should be warmed to body temperature, and injected slowly. The indication for its use is the presence of heart failure which has not responded satisfactorily to other measures.

SPECIAL CONDITIONS

Adherent Pericardium.—Obliteration of the pericardial space by adhesion of the two layers of the pericardium does not of itself give rise to signs or symptoms, and is without clinical importance. But when the two pericardial layers are adherent and the parietal layer is also densely adherent to the ribs, diaphragm, pleura, and mediastinal structures, the work of the heart is enormously increased. For this condition, adhesive mediastinopericarditis, which occurs most often as a result of rheumatic carditis, there is but one form of therapy, namely, surgical removal of a portion of the ribs to which the heart is bound. Obviously, the operation offers hope of relief only if the adhesions to the ribs are those imposing the greatest burden upon the heart, and this is usually the case. There is probably no other group of cardiac patients in which the results of treatment are so brilliant or so gratifying as in those with adhesive pericarditis who are subjected to this operation. The surgical procedure, known unfortunately as cardiolysis, is a simple one, performed under local anesthesia; it is a reproach to American medicine that a therapeutic measure of such great value has been allowed to remain almost unknown. It is true that the diagnosis often cannot be made with confidence, but that does not excuse the widespread failure to think of it and search for it. Fixation of the apex impulse of the heart with changes in the patient's position, systolic retraction of the ribs and interspaces anteriorly, posteriorly, or in the lower left axilla, failure of the left lung to move normally over the anterior surface of the heart during inspiration, and fixation of the electrical axis of the heart as shown by electrocardiograms, are signs which are often easily elicited, and if present, they justify a diagnosis of adherent pericardium.

Great hope has been aroused in some quarters by the daring work of Cutler and his colleagues,[3] who have succeeded in cutting the stenosed mitral valve in the human being. The operation has yet to be proved of value, and the present writer does not share the enthusiasm or the beliefs of those who think it will become an important therapeutic measure.

Coronary Thrombosis.—Thrombosis of one of the branches of the coronary arterial system is becoming more widely recognized as a clinical condition of great frequency. Often the dominant symptom is substernal pain of agonizing intensity, relieved only by large doses of morphin, which should be given without hesitation in whatever doses may be required. It is sometimes necessary to repeat this at intervals for several days. Not infrequently, however, abdominal symptoms dominate the picture, and of these, distention is usually the most distressing and the most difficult to combat. The usual measures recommended for the relief of distention —stupes, rectal tubes, abdominal binders, enemata, etc.,—should be tried if the patient is not too critically ill, but they are often attended with little success. Irrigations of the colon by means of a double tube, the inner and smaller tube inserted for some distance into the sigmoid, have proved of the greatest benefit in some cases. They may be performed without discomfort to the patient or any effort on his part, as the irrigating solution drains into a container on the floor. For the nausea and vomiting that are often present for a few days after the occlusion, there is little that can be, or need be, done, unless the symptoms are caused by distention. If fluids cannot be taken by mouth in sufficient quantities to prevent dehydration, they should be administered daily by injection beneath the skin, in the form of 5 per cent glucose solution and normal saline; amounts of 1,500 to 3,000 c.c. are absorbed by most adults without difficulty. For the increasing difficulty in respiration which is often a feature of these cases, caffein is the best available drug, and may have to be given at intervals of several hours throughout the day. Other symptoms of congestive heart failure, if they appear, should be treated along the lines already indicated.

Cardiac Asthma.—The term cardiac asthma is applied, properly or improperly, to paroxysms of dyspnea, often nocturnal and sometimes of alarming severity. The precise mechanism underlying the seizures is unknown, but there is an intimate relation to arteriosclerosis, hypertension, and angina pectoris. The treatment that usually gives greatest relief is morphin, hypodermically and in full dosage—0.015 to 0.030 gram (¼ to ½ grain). Occasionally, relief follows the administration of the nitrites, especially if the dyspnea is associated with anginal pain. Caffein sodium benzoate is sometimes useful, and venesection, with letting of 500 c.c. of blood, has appeared to be a life-saving measure when the

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[3] See article by Cutler and Beck in this volume.

blood-pressure approached excessive heights. Attacks are sometimes rendered less frequent by the administration of digitalis over a long period.

ANGINA PECTORIS

The drug treatment of angina pectoris may be discussed very briefly. The group of vasodilators known as the nitrites has proved invaluable in this condition, and no other drug except morphin can be regarded as of great value. Of the nitrites, *nitroglycerin* is the cheapest and in general the most effective. The author has never encountered an instance of acquired tolerance to this drug, but it is stated that patients occasionally lose their original excellent response to it. In the event that this occurs, other nitrites usually prove effective, and sooner or later nitroglycerin may again be used. Amyl nitrite in pearls is quite effective, but most patients object to it because its use causes discomfort to others and attracts attention to the sufferer. Sodium nitrite and erythrol tetranitrate have no advantages over nitroglycerin.

Nitroglycerin is preferably given in the form of the soluble tablet, and the patient should have them always within arm's reach. They are dissolved beneath the tongue; relief from pain comes usually within one to three minutes, and lasts for a period varying from a few moments to several hours. The dose that is effective in most individuals is 0.00065 to 0.00130 gram (1/100 to 1/50 grain), but larger doses should be used without hesitation if the smaller ones do not give relief. If the pain persists despite rest and adequate doses of nitrites, closure of a coronary artery should be suspected.

It goes without saying that the life of an anginal patient should be most carefully directed; every form of activity, mental or physical, that evokes the anginal pain should be reduced to the absolute minimum. Hearty meals should be avoided, and exertion should never be undertaken immediately after eating.

Theobromin and *theophyllin* have long been recommended as useful in the treatment of angina, and more recently *euphyllin* (theophyllin ethylenediamin) has been highly praised, especially by Musser. The author has had only a limited experience with these drugs, but has not found them of value in the few patients who took them.

The *surgical treatment* of angina pectoris,[4] hailed with enthusiasm several years ago, now appears to be falling into disfavor. The reasons are not far to seek. There is wide disagreement as to the rationale of the operation, the physiology and even the anatomy of the nerve structures to be divided. The technic of the operation has varied widely. As time has permitted an analysis of end-results, it has become apparent that many patients

[4] See the article by Brown in this volume.

have benefited little if at all. Some have been temporarily relieved, only to have the anginal pains return; some have obtained no relief; some have actually been made worse; a few have apparently been completely and permanently relieved. It is quite possible that better understanding of the sympathetic nervous system will lead to more satisfactory operative results, but at the moment it is a form of treatment to be recommended only after mature deliberation. For details of cases the reader must be referred to the original reports.

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CHAPTER XLIV

THE SURGICAL TREATMENT OF ANGINA PECTORIS
Philip King Brown

To François Franck, a French physiologist, belongs the suggestion that angina pectoris resulted from the irritation of the cardiac aortic plexus from a hypersensitive and diseased aorta. The communicating routes to the brain were by the cervicothoracic sympathetic to the medulla through:

1. Paravertebral chain
2. Vertebral nerves
3. Communicating dorsal branches of the first thoracic ganglion or the fusion of the last cervical ganglion with this

Spasm of the arteries of the medulla was considered by him to be the cause of sudden death and the origin of the spasm lay in the aortic irritation. Vasoconstrictor action of the cervical sympathetic on the bulbar vessels by way of the vertebral nerves Franck considered well established and if the cervicothoracic sympathetic ganglion on one or both sides were resected, he considered that pain would be suppressed and death averted. Franck's article, "Signification physiologique de la resection du sympathique dans la maladie de Basedow, l'epilepsie, l'idiotie et le glaucome," concludes with a summary in which he says: "Cette notion nouvelle de la sensibilité aortique transmise par le sympathique thoraco-cervical suggerera peut-être l'idée de pratiquer la resection dans l'angine de poitrine."

This reasoning Jonnesco enlarged upon nearly two decades later when, in April, 1916, he removed under local anesthesia, the left middle and inferior cervical sympathetic ganglia and the first thoracic in a thirty-eight-year-old syphilitic who had had five severe attacks of angina in three months and apparently was not improving under antisyphilitic treatment. Four years later Jonnesco reported the case. The patient had had no recurrence of his angina and no further antiluetic treatment. He had refused the removal of the same part of his right sympathetic chain, although Jonnesco expressed himself as believing it a desirable procedure. The explanation of Franck, accepted by Jonnesco, of death in angina from spasm of the arteries of the medulla induced by aortic irritation, and conveyed to the brain by any or all of the three routes referred to, which obviously were interrupted on the left side by the removal of the three ganglia (see Fig. 1), would satisfy all the known facts of the case. Presupposing a dis-

eased aorta and diseased medullary vessels would be more or less neces-
sary, and then one would have to know exactly how the altered blood
supply of the medulla worked to stop the heart. On this point and in
general on the cause of the sudden death in angina, authors disagree.
Clifford Allbutt's theory of vagus inhibition and the Eppinger theory of
a separate depressor nerve given off from the vagus, the nodal ganglion
or the superior laryngeal nerve, as described first in animals by Ludwig
and Cyon, have not satisfied physiological or anatomical investigation,
nor do they meet the clinical facts. The explanation of the attacks, the
mechanism of relief, and the cause of death, must be closely related.
Attacks occur and even death has followed where there is no demonstrable
pathological lesion. Youth is not exempt and forty-two cases of definite
angina pectoris in young people were collected and reviewed by White
and Mudd who added eight more, two of them under twenty years of age.
Most of these cases show pathological condition of the heart. All of White
and Mudd's cases had aortic regurgitation following rheumatic fever, but
a considerable number of the others showed no heart pathology. It is
definitely established that men are more likely to suffer from angina than
women, and to die from it, and the fatal age corresponds to the late active
period of life, when degenerative changes have begun but have not as yet
curtailed activity or interfered with responsibilities. Certain poisons like
tobacco predispose to it. Diabetics are peculiarly susceptible. It is curi-
ously associated with pernicious anemia and the author has studied a
severe case associated with anemia from hemorrhage from esophageal
varices, in which attacks occurred only when hemorrhage had depleted the
patient. Abrams, Brule and Heitz report two cases of angina with myx-
edema, in which an already present hypertension was increased and
attacks likewise, under thyroid medication.

There is a growing tendency to belittle heart pains on the part of the
followers of Sir James Mackenzie, and the dangerous word "pseudo-
angina" has been responsible many times for the postponing until too late
proper consideration of well-defined but not disturbing attacks of pain.
Again Mackenzie has separated a group of cases in which he regards
the anginal symptoms as toxic or neurotic and not of serious import.
Kilgore has championed this view and in a recent careful study of his
cases makes a distinction that some of the Vienna school also hold, that
substernal pain and fear of impending death are essential symptoms in the
diagnosis of angina pectoris.

Our experience leads us to decry all this fine distinction, for the his-
tories of many cases studied carefully ten to twelve years have shown us
too many that have had the minor attacks with years of relief, only to
experience the severe ones later on. The author, in a forthcoming paper,
recounts a case of a physician now seventy-three years old, who has been
observed very carefully for twenty-two years, more than five of which were

spent in a hospital, who in this period has had eight or ten major attacks of typical Heberden's angina induced by effort, one attack of coronary thrombosis, and about eight thousand minor anginal attacks induced by cold, smoking, effort or nervous disturbance, relieved promptly, if severe enough to demand its use, by nitroglycerin. A further interesting fact in this case is that the patient, who is a most careful and accurate observer, has repeatedly stated that the pain in all three types of attacks is of the same character, begins in the same place and radiates to the same parts. The only difference is in the intensity and duration of the pain. Further contributions to the nature of angina were the reports of Berman and Mason, Feil and Seigel, in which they show the electrocardiographic changes in the T waves during attacks, corresponding to well established but more lasting changes such as noted in coronary thrombosis cases.

From these facts and from the prompt relief from attacks by the nitrites, and greater freedom from attacks by the long use of theobromin sodium salicylate, it seems reasonable to assume that Heberden's angina is a vascular spasm in which the coronaries certainly take part. From the location of the cardiac plexus and the substernal pain characteristic of typical cases, the participation of the first part of the aorta in the spasm is a possibility, and both Wenckebach and Allbutt hold this to be the case. The frequency of changes in the intima of the aorta at the coronary orifices is an additional serious matter, as is coronary sclerosis, for any spasm of either such sclerosed aorta or coronary will result in a definitely lessened blood supply to the heart because of that further interference during spasm.

With this conception of angina and its cause of death, and prompted by Jonnesco's report of relief of a case following removal of the left middle, inferior and first thoracic ganglia, it was determined by Walter B. Coffey and the writer to do as little as possible on a selected case that had not responded to medical treatment, and to eliminate—one at a time— the various pathways between brain and heart. Accordingly in the early cases operated upon by Coffey, only section of the main sympathetic trunk and the superior cardiac nerve was done. The relief was so graphic in the first case who had no further attacks, although for several years he had had six to ten a day, that we were confronted with the problem of explaining what had happened.

Sensory fibers for the heart run through the upper thoracic nerves to the stellate ganglion. Whether any fibers run as high as the superior cervical ganglion is uncertain, but it is believed very generally that they do not. We were, therefore, not certain of the physiological result of the sectioning done. It completely relieved the patient, and from a condition of being bedridden for ten months, he returned to his home to pursue a relatively normal life. A later case had immediate relief but had a mild relapse of his disease later on. His superior cardiac nerve had an unusual

source of origin and after consideration of all possible steps, Coffey and the writer decided to try removing the superior ganglion to be sure that all sources of origin of the superior cardiac nerve and any communication to the spinal cord by the cervical branches to the superior ganglion had been destroyed. It was found that the superior cardiac nerve in this case had several sources of origin, and at this time Coffey was able to demonstrate them beautifully by injecting the body of the superior cervical ganglion with novocain. All the connections ballooned out and immediately it was evident that there were not only several roots to the superior cardiac nerve, but numerous heretofore undescribed connections to the vagus. The superior ganglion was removed in toto and the patient's attacks ceased this time for good. Since that time the superior cervical ganglion has been removed in all cases,

During the period of our work following the first publication of five cases in 1923, there appeared several notable contributions to the subject, the report of the work of Eppinger and Hofer stimulated by Wenckebach, the studies of Danielopolu and the critical help to us of S. W. Ranson. The novocain injection into the paravertebral chain was practiced in one case by Danielopolu with temporary success, in relieving his patient of attacks during exercise which invariably produced pains, and the operation of severing these connections to the spinal cord was undertaken. A severe attack was precipitated during the operation and, therefore, operation was abandoned before completion. A discussion of the case can be found in our book on angina pectoris and in the publication of our second group of cases. Since then several efforts have been made to work out a method of blocking pain by local injection of procain, novocain or alcohol (Mandel, Swetlow). Most recently James C. and Paul D. White, in Boston, report five severe cases in which 85 per cent alcohol followed the procain.[1] Fairly complete relief was secured in two, slight in two others and none in the fifth case. The marked hyperesthesia following the anesthesia in two to four weeks was very disagreeable in two cases but wore off in several weeks. The Horner syndrome followed in the two successful cases. With this procedure which is very simple, we have been able to relieve pain in several cases where it was due to aneurysmal pressure, and in several cases of aortitis, diffuse heart pain not typically angina, and in a few cases of angina in which low blood-pressure and evidence of coronary disease and myocardial change in the altered cardiographs, made operation inadvisable. A curious fact is that the simple injection of novocain may produce long continued absence of pain. It has even been permanent in some cases. Langley's suggestion to Coffey that the distilled water used in the novocain might destroy sensory fibers, is significant.

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[1] See article by White in this volume.

A persistent apex pain after coronary thrombosis in one case was considered to be due to pericardial adhesions and a constant pull on the heart. Severing the left phrenic nerve relieved this pain of two years' standing.

There remain to be discussed various other modifications of sympathectomy done by surgeons in all parts of the world. First must be mentioned a case of right-sided radiation of pain reported by the writer in which the removal of the right superior sympathetic cervical ganglion was followed by complete relief. Then Kappis and Bruning reported cases where the three cervical and the first dorsal ganglia on the left were resected with relief. In Kappis' case the attacks recurred in four months. Hofer severed the "depressor vagi"; two on the left side and three on both sides. One patient died and the rest were relieved. Kappis quotes Borchard as resecting the left depressor and the lower half of the left superior ganglion to and including the upper half of the middle cervical ganglion. His patient died in three weeks. Danielopolu, conscious that no operation has been a complete success in all cases, has figured it out that one must do a two-stage operation and sever the connections with the spinal column and any vagus connections (Hofer's depressor nerve which, Humber feels, is the cardiac nerve of the vagus and sympathetic in origin) and then cut the cervical ganglion connections with the cardiac plexuses.

There have been successes and failures by every method, but a greater percentage of successes by the method of Coffey and Brown, although by no means free from danger, or universally successful even done on both sides. The fact stands out, however, that no other more extensive operation has accomplished any more, recurrences have come even when the entire left chain was removed, and operations on widely differing tracts have relieved pain (Kappis). We are conducting experiments on the cardiac nerves of the sympathetic with reference to constrictor action. It would be saner to stop what produces pain and death than to interrupt pathways of pain transmission, and if angina is to be robbed of its danger, *the end must be sought that will stop what causes the pain.* The success of the Coffey operation in a large group, and its relative simplicity, recommend it above any other, and although it is not an ideal procedure, it offers the simplest, safest and thus far the most satisfactory results.

The operation for removal of the superior cervical sympathetic ganglion by W. B. Coffey under local anesthesia is done as follows:

Localization of the superior cervical ganglion precedes the making of the incision. The localization is accomplished by the following method: With the patient on his back, the head should be in extreme extension and the face turned toward the opposite shoulder. A sand bag placed crosswise under the shoulders aids materially in attaining the desired position of the patient. With the head in position already described, two lines are drawn (Coffey's lines). The first line, A—B, extends from the anterior part of the lower border of the mandible, backward along the lower margin
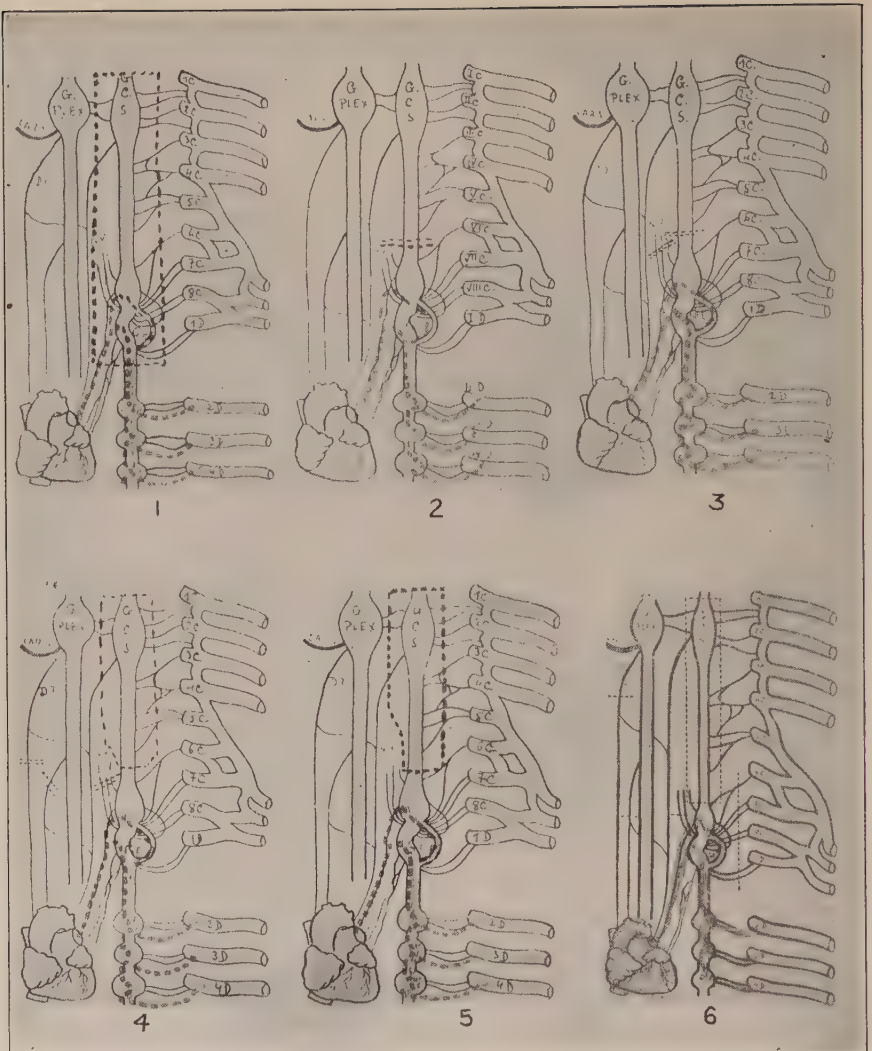
Methods of Sympathectomy.

(D. Danielopolu, Bucharest)

Fig. 1.—Jonnesco's first operation: Complete extirpation of the left cervical sympathetic chain and the first ganglion of the thoracic.

No vagus connections disturbed except connections between the superior cervical ganglion of the sympathetic and the nodal ganglion of the vagus.

Fig. 2.—First operation by Coffey and Brown: Cutting trunk of sympathetic below the superior ganglion and the superior cardiac nerve.

Fig. 3.—Same as Figure 2 with the omission of the severing of the superior cardiac nerve. Instead, the branches of the vertebral ganglia were severed. Danielopolu refers to this operation and states that it was performed with benefit by Gino Pieri of Belluno.

Fig. 4.—The operation as done by Lilienthal, cutting the vertebral connections, the vagus connections (depressor and cardiac nerve of the vagus) besides removing the superior ganglion.

Fig. 5.—Second operation by Coffey and Brown: Removing the superior cervical sympathetic ganglion in order to be sure to secure all the sources of origin of the superior cardiac nerve. It was found that in one of their first group of five cases, the attacks re-

of the bone through the point of conjunction of the inferior margin of the mandible and the posterior margin of the ramus of the mandible (angle of the jaw). This line is continued straight out on the head. The second line, C—D, extends from a point on the postglenoid process of the middle root of the zygomatic process of the temporal bone. This point is found by moving the mandible and putting the finger just posterior to the neck of the condyle of the mandible as it is felt in motion. The middle root forms the upper posterior boundary of the mandibular fossa in which the condyle of the mandible articulates. Line C—D extends to a point on the superior border of the clavicle four and one-half centimeters from the sternoclavicular articulation. Using the point of intersection of lines A—B and C—D as the center, draw a circle three centimeters in diameter. The ganglion lies within the area of this circle. It is very important to keep in mind two points. First, the head should be in extreme extension as described. Second, the mouth must be closed and teeth closely approximated. The use of Coffey's lines makes the localization of the ganglion accurate and not difficult. A free incision is made along the line or just to the side of line C—D through the skin and subcutaneous tissue down to the sternomastoid muscle, care being exercised not to sever the great auricular nerve crossing the muscle obliquely from below upward. The muscle is separated in midline with the handle of the scalpel. The deep cervical fascia is now exposed with the nerve to the sternomastoid muscle coursing across the field from above downward. The identification of the carotid sheath is next. After the sheath is identified it is held above and below with a hemostat. Very careful dissection is required in finding the sheath and separating it at this stage of the operation, extreme care being taken that the sympathetic ganglion is not in such intimate contact with this sheath that it is retracted with it. The proximity of the nodal ganglion of the vagus and the origin from it·of the superior laryngeal nerve helps identification. The superior sympathetic ganglion is larger and its connections are more numerous. They can be determined easily by a procedure used by Coffey of injecting the sheath with novocain which causes the ganglion and its offshoots to balloon out and become quite increasingly blanched, so that the superior cardiac nerve and its one or many sources of origin are made very plain. Humber's dissections show how confusing the situation may be, and if

turned in modified form and were relieved entirely by a second operation in which the ganglion was removed in order to get all sources of origin of the superior cardiac nerve.

The dissection shown in Figures 7 and 7-A, illustrates how easily an incomplete severing of the superior cardiac of the sympathetic may be, if all its sources of origin be not exposed and severed. In the illustration there were four such filaments, one of them arising really at the extreme top of the ganglion.

FIG. 6.—Resection of the superior and middle cervical sympathetic ganglia (but not the inferior and the first dorsal), the vertebral connections, the branches to the heart from the vagus and the lower two cervical and first dorsal rami communicantes. Leriche reported one such operation, in July 1925, with excellent results.

one is not exceedingly careful, the cardiac nerve of the vagus may be confused with the cardiac nerve of the sympathetic. As this is probably the nerve cut by Hofer in his operation with Eppinger under the idea

FIG. 7.—SHOWING ALL THE CONNECTIONS OF THE SUPERIOR CERVICAL SYMPATHETIC GANGLION.

The double lines indicate what was severed in the first operations of Coffey and Brown and the heavy oblong (avoiding the superior laryngeal) what was removed in the later operations. (From *Angina Pectoris*, Coffey, Humber and Brown.)

that it is the depressor nerve, it is important to be sure that it be not mistaken for the superior cardiac nerve of the sympathetic. Hofer has described six or seven different sources of origin of his depressor nerve, and

Humber shows that this variation is true of the superior cardiac nerve of the sympathetic. The cardiac nerve of the vagus is never found outside the sheath of the vagus until it becomes the superior cardiac nerve
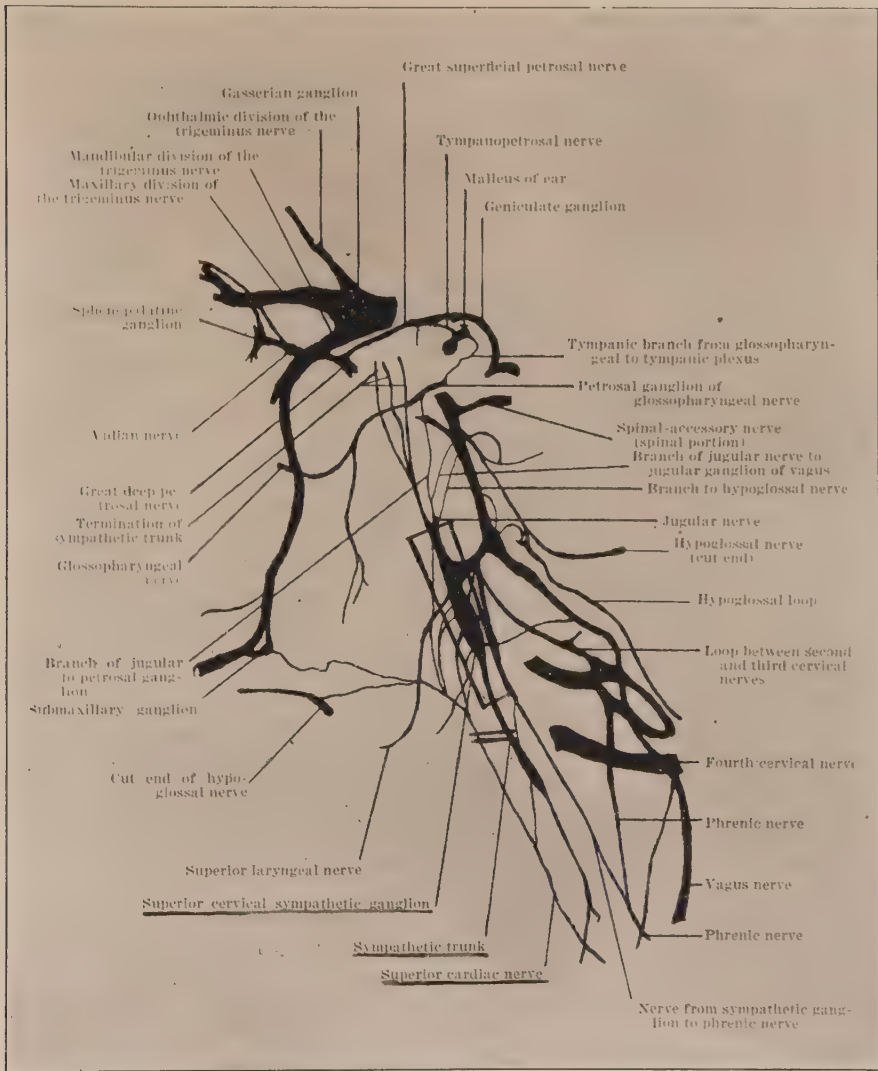
FIG. 7-A.—OUTLINE OF FIG. 7.

of the vagus (a sympathetic nerve) emerging lower down, to contribute to the formation of the cardiac plexuses.

A separate depressor nerve in man is denied by anatomists generally. The excision of the superior cervical sympathetic ganglion, which must be above its bifurcation, is accomplished by holding it in a hemostat and

with scissors cutting the internal carotid and jugular nerves as high up as possible, next cutting all the branches and communications, and after lifting the ganglion up, severing the sympathetic trunk and superior cardiac nerve below. Horner's syndrome on the left side which is a result of this procedure is not a marked deformity. It is of small importance and in thirty-five cases it has not been complained of even by women. Pain in the angle of the left jaw with the beginning of chewing and above the center of the upper border of the scapula, has occurred occasionally.

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CHAPTER XLV

PARAVERTEBRAL ALCOHOL INJECTIONS IN THE TREATMENT OF ANGINA PECTORIS

Paul D. White

Introduction.—In recent years the alcoholic injection of nerves and ganglia has been used in the treatment of intractable pain in various parts of the body, and has been particularly applicable to the prevention of recurrent paroxysms of pain. The alcohol acts by destroying sensory nerve fibers and so interrupts the tracts by which pain reaches the central nervous system. It has been a natural step to include obstinate angina pectoris [1] in the group of conditions to be so treated, but the application of this therapy to this kind of heart trouble has been relatively recent and apparently carried out as yet in but few places. Rare but hopeful reports have been published about this new treatment in the last two years. One of these has come from the Massachusetts General Hospital where for some years previous to the introduction of paravertebral alcohol injections, cervical sympathectomy [2] had been offered and carried out in a few cases of obstinate angina pectoris with indifferent success. The new therapy was welcomed as a possible improvement on the old, but it too is still on trial. Until a large series of cases has been followed over a number of years we cannot make final judgment.

The principle involved in the paravertebral alcohol injection for angina pectoris is simply that of the reduction or abolition of pain. So far as we know the mechanism giving rise to this pain is not altered and the heart disease, which is often progressive, is not retarded. The treatment is symptomatic and solely for the comfort of the individual. In the case of cervical sympathectomy it was thought that there might perhaps be an abolition of the mechanism itself which gives rise to angina pectoris, such as an interruption of the sympathetic nerve tracts carrying stimuli to cause a possible coronary spasm. This has never been proved, however, and in at least some cases the cervical sympathectomy has simply reduced

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[1] Angina pectoris must not be confused with transient or constant pains or aches of other nature; it consists of oppression (not sharp pain) almost always substernal, rarely precordial alone, coming as a rule on exertion, stopping on resting and with the use of nitrites, and sometimes radiating to one or both arms.

[2] Cervical sympathectomy has generally consisted in the removal of the left superior cervical sympathetic ganglion, but in some cases the stellate ganglion also has been removed.

the attacks of angina pectoris without abolishing them, and death has occurred from heart failure in the course of a few months to a few years, without any apparent prolongation of life by the operation. If reducing the pain is found eventually to be all that is gained by cervical sympathectomy, it would seem better to substitute for it the simpler process of paravertebral alcohol injections.

Indications.—The primary indication for the paravertebral alcohol injection for angina pectoris is the frequent recurrence of severe attacks of such pain on relatively slight exertion or, when quiet, and not prevented by a satisfactory trial of medical treatment, consisting chiefly of rest. Much depends, of course, on the factors in an individual case. A patient who is comfortable when quiet and who is neither obliged by circumstances, nor especially anxious to be active, does not particularly need the injection, even though relatively slight exertion brings on the oppression. Another patient who must get about some, even at a moderate risk, or who is made very unhappy by complete invalidism, should be offered the chance of improvement by the injection. Also anyone who is tormented even when at rest by recurrent angina pectoris, should consider this therapeutic measure. It is not to be recommended casually and without due consideration in any case since there is some discomfort connected with it, as will be outlined shortly. A patient with but occasional or rare attacks of pain, even though of moderate severity, may desire the injection, but it is not to be recommended routinely for such a case. Now and again it may seem desirable, however, in such a patient under certain circumstances. Of course I assume that the attacks of angina pectoris in such a case are readily controlled by nitroglycerin. For an active man to be without some check on his strenuous life if he has once had angina pectoris may be, as Sir James Mackenzie once said, unwise, but we really have little accurate knowledge on that point.

Contra-Indications.—There seems to be no contra-indication to paravertebral alcohol injection for angina pectoris if one follows the indications just presented. The procedure is simpler than an operation, requires no anesthetic except a local one, and in skillful hands is not painful or fatiguing. It is conceivable that it may be carried out even in the presence of congestive failure or acute coronary thrombosis, but rarely would it be indicated in such cases. It has been done without harm to patients with an old or even a relatively recent history of coronary thrombosis. It would seem to be possible in some patients in whom cervical sympathectomy would prove too great a risk.

Technic.—Since it is the rami communicantes of the upper dorsal nerves that carry to the spinal cord the sensory impulses of pain from the cervicodorsal sympathetic chain, which in turn receives them from the heart itself, it is these rami that are injected. The number to be injected depends somewhat on the distribution of pain in the individual case; the

higher the pain is, the higher are the nerves that should be injected; the lower, with distribution fully down the arm, the lower the nerves; the more extensive, the more nerves to be injected. If the pain is right-sided the injection should be on the right, if on both sides it may have to be bilateral, but as a rule the site and distribution of the angina pectoris are such that the upper five dorsal nerve roots on the left are the ones to inject.

A brief quotation from the report from the Massachusetts General Hospital already alluded to will give most concisely the actual steps in the process of the injection:

"The only special equipment necessary to perform paravertebral block is a well made 10 c.c. glass syringe and a set of thin, sharp needles from 8 to 10 centimeters in length. A small piece of rubber should be transfixed by each needle before sterilizing for use, as a marker of depth. With the patient lying on his right side, as for a lumbar puncture, the back of the thorax and the shoulders are thoroughly cleansed with alcohol and iodin. With a small cotton pledget dipped in acriflavin, the spinous processes of the upper five dorsal vertebræ are palpated and marked. Acriflavin over tincture of iodin gives instantly a jet black color and is an excellent sterile marking medium. A second series of marks is made 4 centimeters to the left of these spinous processes. A wheal is raised at each of these last points by the intradermal injection of 1 per cent procain. Through each wheal an 8 or 10 centimeter needle is advanced perpendicularly to the plane at the back until at a depth of from 3 to 5 centimeters the underlying rib is felt. The needle is then shifted until its tip is felt to slip by the lower edge of the rib and then rotated so that it points caudally and medially 45 degrees. After this procedure it is advanced forward a distance of exactly 2 centimeters. (This is best measured by using the piece of rubber transfixed by the needle as a marker and setting it 2 centimeters away from the skin when the needle point is in contact with the lower edge of the rib.) The tip of the needle which has been inserted in this fashion, should be between the external and internal intercostal muscles and close to the intercostal nerve, artery and vein. One of the vessels may easily be injured, in which case blood will drip from the needle. In this event the needle must be withdrawn and reinserted. Our method has been to insert all five needles, to aspirate each to make sure that it contains neither blood nor spinal fluid, and then to inject 5 c.c. of 1 per cent procain. If the needle point has penetrated the pleural cavity, the injection of procain will make the patient cough. Swetlow [3] connects each needle with a small manometer to make sure that there are no respiratory oscillations. In this event, the position of the needle must be readjusted.

"Within ten minutes of the procain injection there should be anesthesia from the midline in the back to the sternum in front and from the fifth

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[3] G. I. Swetlow, "Paravertebral Alcohol Block in Cardiac Pain," *Am. Heart J.*, April, 1926, 1:393.

intercostal space up to the region where the descending branches of the cervical plexus overlap the three upper ribs. If the first and second dorsal nerves have been properly blocked there should be good anesthesia of the axilla extending a few centimeters down the arm along with the so-called Horner syndrome—a contracted left pupil and narrowed palpebral fissure.

"During this time the five needles have been left undisturbed. As soon as it is apparent that the anesthesia is complete, 5 c.c. of 85 per cent alcohol is injected into each and the needles are withdrawn.

"It is obvious that this procedure requires much practice and that definite harm may result from neglect of any detail. If 5 c.c. of methylthionin chlorid is injected into a cadaver as here described and then cut down on, the dye will be found to have run about 5 centimeters outward along the course of the intercostal nerve and to have diffused centrally into the intercostal foramen, so that it surrounds the sensory ganglion and the rami communicantes of the sympathetic.

"Experimental injection into animals shows that 5 c.c. of 5 per cent alcohol produces a zone of necrosis only about 2 centimeters in diameter. Therefore, in order to obtain a lasting block, the anatomic bearings must be taken with great accuracy in order to get as close as possible to the nerve at the point at which it leaves the intercostal foramen. Practice on the cadaver is an essential preliminary to these injections and should be followed by thorough practice with intercostal procain injections in as many thoracic operations as possible." [4]

Results.—The chance that the paravertebral alcohol injection will help the individual patient is a fairly good one. Of eight cases at the Massachusetts General Hospital relief was apparently complete in three, almost complete in two others, 50 per cent in two more and only slightly effective in one. One of the three cases with complete relief of the left-sided angina pectoris by his first injection had a right-sided injection a year later with no relief at all, but fortunately his right-sided angina pectoris was much less severe than his left had been. Four of the patients had had coronary thrombosis before the injection; none of these four was disturbed especially by the procedure, though two of them died suddenly five and eight months later, respectively, apparently of a second attack of coronary thrombosis. Death is probably not delayed by this treatment, nor is it hastened, but life is made more comfortable.

When we began the series of cases at the Massachusetts General Hospital we thought that even if the alcohol injection were successful, it might be so for but a few months, regeneration of the nerves necessitating another injection, but to date (some one and one-half years in the case of longest duration) a second injection on the same side has not been required.

[4] J. C. White and P. D. White, "Angina Pectoris, Treatment with Paravertebral Alcohol Injections," *J. Am. M. Ass.*, April, 1928, 90: 1099.

Complications.—The subject should not be left without a statement of complications and by-effects of the injection. These are chiefly two: (1) At the time of injection the pleura may be irritated directly by the alcohol; if it is, there may be severe pain and temporary collapse. The pleural pain occurred in three of our cases with transient collapse in two. (2) A common, possibly almost universal sequel of the injection coming on a few days, and lasting for a few weeks afterwards, is some degree of hyperesthesia and pain in the chest wall, left shoulder or left arm corresponding in area to the nerves injected. This may be extremely disagreeable for a few days, but it gradually passes off, leaving, as a rule, no trace. There was a great variation in the degree and extent of this complication in our cases, but it was present in greater or lesser degree in all. It wore away in all cases except on the right side in the one case reinjected for the right angina pectoris a few months ago. This phenomenon of hyperesthesia for a few weeks following the first few days of numbness has been explained by the involvement of the peripheral nerves in the process, there being a transient edema from which the nerves gradually recover with hyperesthesia and pain, but these nerves are not destroyed as are probably the rami communicantes.

CHAPTER XLVI

TREATMENT OF DISORDERS OF THE HEART BEAT
Paul D. White

Introduction.—Disorders of the heart beat are abnormalities of function and therefore their direct treatment actually amounts to symptomatic therapy. The condition underlying these various disorders should of course be diagnosed in every case, for the recognition and treatment of the etiological factor is of prime importance. Nevertheless, it is worth while summarizing certain procedures which are known to be of value in relieving some of these disorders of the heart beat.

Disorders of the heart beat consist of disturbances of sinus rhythm itself, ordinarily called sinus arhythmia, sinus bradycardia, and sinus tachycardia; premature beats, auricular, ventricular, or the so-called atrioventricular or nodal; paroxysmal tachycardia of auricular or ventricular origin; auricular flutter; auricular fibrillation; heart-block, partial and complete; and pulsus alternans.

SINUS ARYTHMIA, SINUS BRADYCARDIA, SINUS TACHYCARDIA

Sinus Arhythmia.—All manner of disturbance of sinus rhythm may occur, from a simple irregularity in rate of the pacemaker in the sino-auricular node to a complete sino-auricular heart-block with auricular standstill. The very common condition of respiratory *sinus arhythmia* is now generally well recognized, but occasionally when exaggerated in a nervous individual it may be confusing. Sometimes it may appear as if the sinus arhythmia were not definitely related to respiration, but a simple test of forced respiration will quickly settle the matter. Normally, forced inspiration produces a definite tachycardia in a patient showing sinus arhythmia, while forced expiration will produce a pronounced bradycardia. This arhythmia is of little importance, certainly not to be treated itself. It is the result of nervous instability in a given patient, the balance between the actions of the sympathetic and vagus nerves on the sino-auricular node being a very delicate one in such an individual. The condition, especially when exaggerated, is very common in young people, particularly between the ages of twelve and twenty-five. It tends to be exaggerated under such conditions as convalescence from infectious disease

and nervous or physical fatigue of any sort. The condition itself is not a sign of health; it is a sign of active response of the heart to nervous stimuli. It has been considered a sign of a healthy heart, but it is found sometimes in badly damaged hearts and the reason is obvious: heart muscle may be diseased and still the heart responds in a normal or exaggerated manner to nervous stimuli. Since, however, young people have less heart disease than old people and since arhythmia is more common in young people than in old people, so it may be said that sinus arhythmia and normal heart muscle are usually associated. There is no treatment indicated for sinus arhythmia, as such.

Sinus Bradycardia.—Rarely one finds the condition of so-called *sino-auricular block,* which consists of a very marked slowing of the rate of the pacemaker in the sino-auricular node (down to 40 or below per minute) generally without any auriculoventricular block, or a dropping out altogether for one pulse interval of any evidence of auricular stimulus or contraction, or very rarely a complete sino-auricular block consisting of a standstill of the auricles. In this last-named condition the ventricle escapes, idioventricular rhythm at a slow regular rate taking the place of the previous normal rhythm. This condition of sino-auricular block, whether simply pronounced slowing of the whole heart or "dropped beats" of the whole heart or complete auricular standstill, is generally the result of digitalis intoxication. It is apparently chiefly the effect of marked vagal stimulation. In thirteen and one-half years at the Massachusetts General Hospital there have been thirty-nine cases; in these, digitalis was primarily responsible in about one-third and quinidin in three; in thirteen patients the block was complete, giving rise to auricular standstill, and in four cases there were dropped beats. In two or three cases there was a very slow sino-auricular rhythm and in one case the sino-auricular rate suddenly halved after exercise. The conduction intervals between auricles and ventricles when present were within normal limits. The condition was transient in all cases, without effect on life.

Treatment.—If digitalis or quinidin is found to be the cause of the sino-auricular block the remedy is obvious: namely, the omission of the digitalis or quinidin. It is probably worth while to try the effect of atropin 1/30 gr. by mouth or even subcutaneously as a therapeutic test in a case of "sino-auricular block," but whether or not repeated doses of atropin or belladonna would tend to abolish the block we have little evidence. In the absence of digitalis a search for other factors giving rise to vagal irritability should be instituted and causes, if any are found, eliminated.

Sinus Tachycardia.—Finally, in discussing variation of rate of the sino-auricular pacemaker, we come to the so-called *sino-auricular tachycardia,* which is simply the rapid rate of the normal pacemaker of the heart, as a rule the result of extracardiac conditions.

Treatment.—Treatment of the tachycardia itself is usually ineffective. An attempt to slow the rate by digitalis or other drugs is probably unwise when the rapid rate is the only disturbing cardiac sign. The condition back of the tachycardia is, of course, what demands treatment. Nearly every infectious disease produces sino-auricular tachycardia. Hyperthyroidism is associated with tachycardia; nervousness gives rise to tachycardia in many people; the toxic effect of uremia results often in tachycardia. Heart failure with normal rhythm may produce tachycardia, but in every instance it is the underlying condition and not the tachycardia which must be treated. As a general rule, rest in bed is the essential therapeutic measure for any of these conditions. Rarely, the tachycardia is of unknown cause and is unaffected by any therapeutic measure, persisting, especially in nervous individuals, even for years without causing harm, and usually subsiding spontaneously. If the pulse rate rises above 150, and remains at a uniform rate, some other mechanism than sino-auricular tachycardia should be suspected. Under such circumstances either paroxysmal tachycardia or auricular flutter is probably the underlying condition.

PREMATURE CONTRACTIONS

Premature contractions of the heart, so-called "extrasystoles," are most commonly ventricular in origin, the ratio of ventricular premature contractions to auricular premature contractions being 753 to 385 (about 2 to 1) in the last thirteen and a half years at the Massachusetts General Hospital. The premature contraction, whether auricular or ventricular, is almost certainly the result of abnormal irritability of the myocardium or of the special conducting tissue. It may be simply a temporary toxic effect associated with indigestion, tobacco poisoning, nervous fatigue or excitement. On the other hand, it may be the result of definite change due to myocardial disease as in arteriosclerosis or rheumatism. It may occur rarely, only a few times in the course of days or weeks, or it may come so often that it produces a bigeminal or coupled pulse, every other beat being a premature contraction. In rare cases, there may even be more premature contractions than normal beats of the heart. Of course, the more often the premature contractions occur the more evidence there is of irritation and irritability of the myocardium. In themselves premature contractions are not evidence of heart disease; they are simply evidence of an irritable or irritated heart. There are records of patients who have shown premature contractions for a great many years without any appreciable heart disease. Mackenzie reports the case of a patient, a man of sixty-nine, who came to him complaining of premature contractions of the heart which had occurred at frequent intervals for over fifty years, causing much distress of mind because of the failure properly to recognize the

significance of these premature beats. Even at the age of sixty-nine this man was in fairly good health except for the premature contractions.

Treatment.—It is obvious that in the treatment of premature contractions the underlying cause should be ascertained. This is not always possible, but in at least half the cases clues can be found and the omission of some such offending factor as tobacco, overwork or anxiety may result in the disappearance of the premature beats. Sometimes in the case of heart disease attended by premature contractions, rest and digitalis will result in disappearance of heart failure and the premature beats associated with it. On the other hand, digitalis may itself induce premature contractions if given in large doses, particularly to persons with irritable hearts. Such premature contractions may be either auricular or ventricular and are a sign at the height of digitalis intoxication that the drug should be stopped. If the typical bigeminal pulse appears during the administration of a good deal of digitalis it is probable that a high percentage of the lethal dose has been administered.

Thus there is no set rule about the treatment of premature contractions. Sometimes if heart failure is present digitalis will cause the premature contractions to disappear, and sometimes it will produce them. If treatment of the underlying condition or the institution of proper hygiene in a person who has lived unhygienically fails to abolish the premature contractions, it may be worth while to try drug therapy. Bromids in a few cases seem to help, and it has been recently suggested that quinidin sulphate given in doses of 3 to 6 gr. (0.2 to 0.4 gm.) several times a day may clear up the premature contractions. Certainly quinidin sulphate is ineffective in some cases, but in other cases the premature contractions have disappeared under its administration at the same time that there has been an increase in pulse rate. Further work in the use of quinidin sulphate in the treatment of obstinate premature contractions must be done to establish its value. The matter still remains unsettled to date. Generally quinidin sulphate appears to be ineffective in abolishing premature beats.

Summarizing the therapy of premature contractions, it may be said that the underlying factor is to be searched for and treated. The frequent failure to discover and remedy the underlying cause makes it advisable at times to try therapeutic measures such as the administration of bromids or quinidin; but, as Mackenzie has said, not infrequently, regardless of the therapy instituted, premature beats will persist for many years and not incapacitate the individual showing them. Reassurance is very frequently an important measure in the treatment of a person bothered by the palpitation of premature beats. Mackenzie finishes his discussion of the treatment of "extrasystoles" by saying that some people have premature contractions more often when they are leading sedentary lives

indoors. Therefore he advises for such people more exercise in the open air.

The separation of premature contractions into auricular, ventricular and nodal has little if any significance in regard to treatment. It is thought that auricular premature contractions, although much more rare, are more significant evidence of cardiac irritability and are apt to precede such conditions as paroxysmal tachycardia or auricular fibrillation or flutter. The atrioventricular or nodal extrasystoles are very rare and consist essentially of an escape of the ventricular pacemaker due to excessive irritability of the atrioventricular node. Digitalis may be responsible for some of these cases.

PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia consists in sudden acceleration of the rate of the heart, lasting seconds, minutes or hours, and stopping abruptly. The condition is due to the inception of abnormal rhythm by some irritable focus in the auricular or ventricular myocardium. The rate of this abnormal pacemaker ranges usually between 120 and 200 and a very frequent rate is in the vicinity of 160 per minute. Auricular paroxysmal tachycardia, that is, the abnormal rhythm resulting from an irritable focus in the auricle, is much more common than the ventricular type of paroxysmal tachycardia, the ratio at the Massachusetts General Hospital in the last thirteen and a half years being 78 to 11 (7 to 1). Why this is so is not known, since ventricular premature beats are so much more common than auricular premature beats, and it is ordinarily considered that paroxysmal tachycardia consists of a rapid repetition of premature contractions. Certainly further investigation of the fundamental mechanism of premature contractions and paroxysmal tachycardia is essential to clear up this point. Clinically, the underlying causes of paroxysmal tachycardia are just the same as those for premature beats. Paroxysmal tachycardia may occur in organic heart disease and is not infrequent in cases of thyroid heart disease, arteriosclerotic heart disease or rheumatic heart disease, but it is much more commonly found in the absence of organic heart disease and in the presence of irritability or irritation of the myocardium. Again, toxic influences such as digitalis, tobacco, indigestion and fatigue may produce paroxysmal tachycardia.

General Treatment.—The treatment of paroxysmal tachycardia consists in the discovery and omission of the exciting cause. Here, as in the case of premature contractions, it is not infrequently impossible to ascertain the etiology. Then symptomatic therapy must be instituted, and there are almost as many methods recommended for the immediate treatment of paroxysms of tachycardia as there are patients who have paroxysmal tachycardia. A good many victims have discovered and

utilize their own methods for stopping attacks, and nearly every textbook in discussing paroxysmal tachycardia gives a list of methods which have been found of value in stopping the attacks in various individuals. Most of these methods depend on the reflex stimulation of the vagus nerve and probably the cases successfully treated under almost any method are those in which the abnormal pacemaker is more under the influence of the vagus nerve than it is in the cases which fail to be influenced.

Some of the procedures which have been used with success are, in brief, as follows: vagal pressure on either side of the neck, consisting of firm digital compression of the carotid artery midway in the neck (compression of the carotid artery to the point of occlusion of the vessel will produce stimulation of the vagus nerve which lies in the carotid sheath under the artery); and pressure of the eyeball on either side with the eye closed, up to the point of pain. Both these measures are of more value than all the other procedures put together and they certainly should be tried in every case of paroxysmal tachycardia. Pressure on the vagus nerve, if successful, usually is effective in less than a minute, sometimes in a very few seconds; similarly with regard to ocular pressure. The vagal pressure is a direct stimulation of the vagus nerve while the ocular pressure resulting in the oculocardiac reflex is a result of indirect reflex stimulation. It has been recently suggested that the so-called vagal pressure really causes a vagal reflex by compression of the carotid artery itself. These measures are effective in probably one-third of the cases of paroxysmal tachycardia. Some patients can be taught to compress their own vagus nerve at the onset of an attack of paroxysmal tachycardia and so control the condition themselves without the need of calling a physician. Other procedures, mostly affecting the heart through vagal reflex action, are the induction of vomiting, repeated swallowing or the swallowing of a considerable amount of cold water, an attempt at forced expiration with the glottis closed (the so-called Valsalva experiment), holding the breath as long as possible, leaning over backwards with the neck extended (resulting in stretching the tissues of the neck), firm compression of the abdomen or chest by a swathe, ice-bag to the epigastrium or precordia, and finally leaning forward with the head very low. All these measures have resulted in stopping paroxysms of tachycardia in different individuals. Sometimes the same procedure will be effective repeatedly in a given person and sometimes one of these procedures will be effective in the treatment of paroxysmal tachycardia in several different individuals. It is doubtful whether the type of paroxysmal tachycardia, that is, auricular or ventricular, is of importance in relation to the therapeutic measure to be used.

Drugs.—A word should be said about the drug therapy of paroxysmal tachycardia. Digitalis has been given intravenously, subcutaneously and by mouth to patients with paroxysmal tachycardia. Strophanthin has also

been used, morphin has its advocates, and now quinidin sulphate is being recommended. Certainly in some patients with paroxysmal tachycardia the attacks have stopped very soon after the administration of some of these drugs. It must always be borne in mind, however, that paroxysmal tachycardia stops spontaneously and that an attack may stop spontaneously within a short time after the administration of some drug. If, however, the patient has paroxysmal tachycardia, usually of a fairly definite duration and repeated, and the administration of some such drug as digitalis, morphin or quinidin sulphate results in a marked shortening of the attack, it is reasonable to suppose that the drug has had an effect. One must view all remedies, however, very critically. At the present time it is believed that quinidin sulphate in some cases does stop attacks of paroxysmal tachycardia. The dosage should be 6 gr. (0.4 gm.) at two-hour intervals in a person who is not susceptible to quinidin intoxication. (The test for susceptibility consists of administration of 3 gr. (0.2 gm.) with observation as to the appearance of headache, nausea or tinnitus for the next few hours.) At the Massachusetts General Hospital we have had success and failure in about the same number of cases in the administration of quinidin to stop paroxysmal tachycardia, but the series is small (about twelve in all). That has been the general experience elsewhere, so that the present status of quinidin therapy in paroxysmal tachycardia is uncertain. Further investigation should be carried on. Quinidin sulphate or quinin hydrochlorid intravenously has also been used successfully to stop paroxysms of auricular or ventricular tachycardia. One more point should be mentioned regarding the use of quinidin sulphate, and that is that the daily rationing of from 3 to 12 gr. (0.2 to 0.8 gm.) may be of some value in the prevention of paroxysms of tachycardia.

Finally atrioventricular paroxysmal tachycardia, or nodal paroxysmal tachycardia as it is sometimes called, is very rare. The treatment would be the same as for the other types.

AURICULAR FLUTTER

Auricular flutter and auricular fibrillation are closely allied conditions, but since there is some clinical importance in differentiating them they will be discussed here separately. Auricular flutter consists of a very rapid regular contraction of the auricle at rates between 200 and 400 with the ventricular response usually at one-half the auricular rate, that is, with 2 to 1 heart-block accompanying the auricular flutter. The reason for the heart-block is obvious. The auriculoventricular conduction tissue is unable to transmit, as a general rule, every auricular impulse. Rarely does one see a patient with auricular flutter without block, in which every stimulus descends to the ventricle, even at rates close to 300. The important work of Thomas Lewis in recent years in analyzing the mechanism

of auricular flutter and auricular fibrillation has demonstrated that auricular flutter is due to a circus movement in the right auricle. This circus movement consists of a contraction wave traveling rapidly along a band or bands of muscle around the great veins. Apparently a certain degree of irritability of the auricular muscle is necessary before this circus movement is initiated. This degree of irritability is dependent, as a rule, on definite cardiac disease and so auricular flutter is seen chiefly in two conditions: arteriosclerotic heart disease and rheumatic heart disease. Rarely it may result from other conditions such as temporary toxemia. Hence auricular flutter is of more clinical significance, in other words, a more important sign of heart disturbance, than is paroxysmal tachycardia, and its mechanism is quite different so far as we know at present.

Treatment.—Some years ago Ritchie and others described what has been a classical method of treating flutter. Upon the discovery of the condition by electrocardiogram or jugular pulse tracing, for it cannot be proved by other methods of examination, the heart is saturated with digitalis. The first effect from the digitalis is the increase in the degree of heart-block so that 3 and 4 and even 5 and 6 to 1 auriculoventricular block results. Sometimes this block occurs regularly so that the ventricular rate will suddenly drop from 150 to 75 for example, and sometimes the block will be irregular in grade so that a high degree of arhythmia results from the rapid succession of grades of block varying from 2 to 1 up to 6 to 1. By careful analysis of the pulse even these irregular grades of block can be analyzed correctly through the law of dominant rhythm. If the digitalis is pushed to a still further degree, perhaps up to the point of gastro-intestinal discomfort, auricular fibrillation is instituted in a considerable percentage of the cases. As soon as auricular fibrillation appears the digitalis is discontinued and in certain cases normal rhythm quickly results. However, in a certain number of patients this classical method of treatment does not have the results expected and on stopping the digitalis the auricular fibrillation may persist or flutter recur. In spite of the failure in many cases of auricular flutter to yield properly to digitalis, digitalization is still the method of choice in therapy, for even though the auricular flutter is not abolished, the ventricular rate is controlled by the production of block. With a regular ventricular rate of 75 to the minute proper circulation can be maintained indefinitely even though the auricles are continuing their contractions at the rate of 300 a minute. Maintenance of digitalization would be necessary to cause this effect to persist. The procedure for maintenance of digitalization would be the same as that to be described shortly under auricular fibrillation. Moreover, even if auricular fibrillation is produced by the digitalization of auricular flutter, it may be controlled, so far as ventricular rate is concerned, by the maintenance of the digitalization.

Since the introduction of quinidin sulphate, a new method for the treatment of flutter has been instituted. In some cases the drug has been effective in abolishing the flutter. In other and more frequent cases, the flutter has persisted in spite of the quinidin and has even been made apparently more obstinate in its reaction to digitalis, which was tried later. The treatment of flutter by quinidin is similar to that of fibrillation by quinidin.

The principles of the treatment of auricular flutter are two in number: first, attempt to abolish auricular flutter altogether with a restoration to normal rhythm, whether by the use of digitalis or quinidin; second, if the first procedure is impossible, control the ventricular rate in auricular flutter by proper digitalization. It must be borne in mind, however, in conclusion, that auricular flutter is often paroxysmal and may stop spontaneously. If the attacks are very brief, as sometimes happens, neither digitalis nor quinidin would have time to get in an effect before the attack is over. It should be said, however, that paroxysms of auricular flutter, just as paroxysms of auricular fibrillation, may be decreased in frequency and even abolished altogether for a considerable length of time by rations of quinidin sulphate. Quinidin sulphate either in tablet or capsule form, 3 gr. (0.2 gm.) at a dose, and from 3 gr. to 12 gr. (0.2 to 0.8 gm.) a day, is effective in some cases in the prevention of paroxysms of auricular flutter. Therefore, in a patient who shows paroxysms of auricular flutter it is worth while to try the effect of quinidin sulphate as a prophylactic. If the attack of auricular flutter has become well established either digitalis or quinidin sulphate may be tried. At the present moment it is probably wiser to use digitalis by and large. It is desirable that each case should be tried individually, for some patients will react to quinidin better than others and it may actually be injurious to some if quinidin therapy is persisted in after early failure to react.

AURICULAR FIBRILLATION

Auricular fibrillation is a very common disorder of the heart beat, very much more common than auricular flutter clinically, probably seen twenty times more frequently. As a matter of fact, as the investigations of Thomas Lewis and his collaborators have shown, the mechanism behind the two conditions is the same, but auricular fibrillation is a higher grade and more prominent type of the disturbed mechanism than is auricular flutter. In the case of auricular fibrillation, the so-called circus movement which travels very rapidly around the great veins of the right auricle reaches such a speed that it no longer travels uniformly but becomes very irregular in its course and rate. Auricular rates of 500 or more are not infrequent in auricular fibrillation. The ventricles respond irregularly and rapidly to the circus movement of auricular fibrillation so that clin-

ically there is a sharp distinction between auricular flutter and auricular fibrillation. There are occasionally border-line cases in which by electrocardiogram auricular activity is seen to be not quite regular and yet closely resembling flutter. This condition is sometimes called impure flutter or coarse fibrillation. Such border-line cases would be expected to occur. Their treatment is similar to that for auricular fibrillation.

Absolute arhythmia, which is the old term given to auricular fibrillation, may be paroxysmal or permanent. It is generally a sign of serious or important heart disease. Rarely it is found in hearts that are otherwise apparently normal. The most common etiological causes for heart disease associated with auricular fibrillation are coronary arteriosclerosis (abbreviated to *cardiosclerosis*), rheumatic heart disease and thyroid heart disease. Although auricular fibrillation is almost always a sign of extensive heart disease it may be borne for many years, and cases are on record who have shown absolute irregularity of the pulse for twenty or thirty or more years.

The chief reason, clinically, why auricular fibrillation is a burden to the circulation is not because the auricle contracts ineffectually but because the ventricular rate is high. The ventricular contractions are so rapid and irregular that the circulation is badly disturbed.

Digitalis Therapy of Auricular Fibrillation.—There are two methods of treating auricular fibrillation. The first, which is in general the one widely accepted and which should be continued in most cases, is by the use of digitalis. By the digitalization of a patient, that is, by the saturation with digitalis, there results a depression of the conducting mechanism of the heart. The ventricles can no longer respond to so many rapid irregular stimuli from the auricle, and the partial block which is already present is increased. When the increase of block has reached such a point that the ventricular rate is reduced from its original 120 to 160 down close to a normal figure, 70 to 80, the circulation improves tremendously. Improvement of the circulation is due almost entirely to the more effectual contractions of the heart. When the heart is contracting irregularly at the rate of 160, the force of many of the beats is so slight that the pulsations do not reach the periphery of the body. Hence the contractions of the heart are wasted and much needless work is done. Particularly is this injurious to the heart and circulation if the myocardium is diseased, as it is in most of the patients who show auricular fibrillation. The heart muscle becomes tired and a vicious circle is instituted. Congestive failure results, and unless the ventricular rate is cut down the patient may die of heart failure. By the simple reduction of the heart rate from 150 to 75 a minute by the use of digitalis in auricular fibrillation, 75 beats a minute are saved. The work of the heart is reduced one-half. In the course of twenty-four hours 108,000 contractions of the heart would take place instead of 216,000; there would be a saving to the heart of 108,000

beats a day. This must mean tremendous rest for the heart, and it is that rest with improvement in the force of contractions that restores the circulation so rapidly and dramatically in patients with auricular fibrillation and congestive failure, who have been previously improperly treated. To be sure, digitalis also acts by increasing the degree of systolic shortening of the heart muscle, and so digitalis often has a beneficial effect in cardiac congestive failure when the pulse is normal and slow. This effect would be produced in auricular fibrillation as well as in normal rhythm, but without doubt the most important benefit from digitalis in auricular fibrillation is through the rapid reduction of the ventricular rate. And also without doubt the great reputation that digitalis has obtained throughout the world results from its toxic effect on the conducting tissue and its production of heart-block in auricular fibrillation and not from its stimulating effect on the myocardium. It is surprising to find how few doctors recognize the importance of this point, although Withering called attention to it over a century ago. The principle of digitalization has only recently become understood by any considerable percentage of practicing physicians.

The principles of digitalis therapy in auricular fibrillation are as follows: first, saturation of the patient with the drug; second, maintenance of saturation as long as necessary. Saturation of the patient with the drug is dependent on several conditions. First, a drug of proper potency is necessary. Fortunately at present most digitalis preparations on the market, if fresh, have been standardized and are within reasonable range of normal strength. If, however, digitalis is used which has been on the shelves of a country pharmacy for some years there may be very little value left in the drug. If in doubt, it is wise either to have preparations of digitalis which are to be used standardized and fresh, or else to use trade preparations which are known to be well standardized. The second point in regard to saturation of a patient with digitalis concerns the time during which saturation can be effected. It is no longer necessary to wait one, two or three weeks before the patient is under the control of the drug. We now know that we can saturate almost any patient in the course of hours, or a day or two at the most. Rarely is there so much urgency that saturation must be effected within a few hours. If such a case is being treated the large Eggleston dosage is advisable. According to the Eggleston dosage the amount of digitalis necessary to saturate is figured up according to body weight; from 0.1 to 0.15 gm. of a potent leaf for 10 pounds of body weight is the standard. After calculation of the total amount necessary for saturation by this method, from one-third to one-half the total amount is given at once; in six hours one-sixth to one-fourth more is given; in six more hours, one-eighth of the total dose, and so on until the patient's pulse rate has been reduced close to normal limits or until other toxic symptoms have appeared, such as nausea and vomiting

or a bigeminal pulse. The majority of patients do not need such rapid saturation, and in the course of two or three days enough digitalis may be given to control the ventricular rate. For example, 3 gr. (0.2 gm.) three or four times a day for two or three days, will generally produce a sufficient effect quickly enough without running quite so much risk of the production of nausea and vomiting in a sensitive person. It is important to judge the amount of digitalis by the weight of the individual, although a rough estimate may be sufficient in most cases, people of average weight (120 to 180 lbs.) being controlled by about the same dosage. Occasionally, as a therapeutic test in a patient who may not be under close control but who is to be seen in one week, say in a dispensary cardiac clinic, or in private practice, 1½ gr. (0.1 gm.) three or four times a day for one week may be prescribed. In the course of a week such a patient will generally be saturated, and when he returns to the clinic one can decide whether or not there has been benefit from this procedure of a rather slow saturation.

In the discussion of the digitalis treatment of fibrillation I have spoken of grams of the leaf. Of course cubic centimeters of the tincture of a good digitalis leaf may be used instead, at ten times the figure computed for the dry leaf. For the infusion made from the tincture the amount must be still further multiplied by ten. An important point should be brought out here regarding the use of the tincture. Very often I have seen the tincture prescribed in drops when minims were intended. We know that as a rule it takes 2 to 3 drops of the tincture of digitalis to make 1 minim. Therefore, unless this point is recognized and sufficient dosage is ordered to make up the minims planned, or unless a minim glass is available, the use of the tincture is uncertain. The measurement of drops is cumbersome and the carrying about of the tincture of digitalis is not so simple as the carrying of the dry leaf in pill form, each pill comprising 1½ gr. (0.1 gm.), a very convenient amount for calculation and administration. It is possible that the tincture of digitalis in some patients may be better absorbed than the dried leaf, but for some years, at the Massachusetts General Hospital, the dried leaf in pill form has been used to a great effect without any appreciable difficulty concerning absorption.

Digitalis may be administered intravenously, subcutaneously or rectally in the same dosage as by mouth if there is vomiting not the result of digitalis.

Another point may be brought up concerning the use of digitalis in auricular fibrillation, and that is the relative value of the proprietary preparations and a simple leaf in pill form. If the leaf is well standardized there is little need to call on any of the expensive proprietary preparations. Eventually, when we have learned what the important active principles of the digitalis leaf are and have a preparation containing

simply those principles, we can dispense with the whole leaf. Until that time I think the simplest procedure in digitalis therapy is the use of the leaf in pill form.

Rarely is it necessary to administer digitalis intravenously or intramuscularly, subcutaneously or rectally. Once in a while in an urgent case such a therapeutic measure is advisable. Under such circumstances a preparation of digitalis leaf in the dosage of 1½ gr. (0.1 gm.) to 7½ gr. (0.5 gm.) in solution in an ampule may be administered intravenously at intervals far enough apart so that intoxication will not occur unexpectedly, symptoms and signs of intoxication to be observed before the next dose is given. Digitalis may in this way be given every three to six hours with care. It is, however, not more than once in a hundred times that it is necessary to use digitalis intravenously. Under such circumstances strophanthin may also have a place, although it probably does not act in equivalent strength more quickly than digitalis. The dosage of 1/60 gr. (1 mg.) is dangerous for ordinary use; 0.5 mg. to 0.25 mg. is as much as should be given at a time. In the use of any intravenous preparations or in the administration of large amounts of digitalis orally, care should be taken that the patient has not already been taking digitalis in appreciable amount.

The second main principle in digitalis therapy is the maintenance of digitalization when it is indicated; in the treatment of auricular fibrillation, when it has been decided not to try the effect of quinidin sulphate, such a procedure is almost invariably necessary. After saturation with digitalis, when the ventricular rate has been reduced to about normal, this rate may be maintained for days, weeks, months or years by proper rationing with digitalis. As a rule it has been found that if as much digitalis is given every day as is excreted, this equilibrium can be maintained. Pardee and others have found that about 0.1 gm. of digitalis is excreted by the average adult every day. Therefore, the administration of this amount 1½ gr. (0.1 gm.) every day for years will maintain a good pulse rate for this length of time. Occasionally, individual patients will find that this amount is too much, that is, they will become toxic when using it. If so, they may occasionally omit the digitalis for a day, or take it every other day. Also, occasionally patients will be found who do not get enough digitalis in this way to maintain saturation. Such patients will need an occasional extra pill, sometimes as much as two pills a day. The various other members of the so-called digitalis group, strophanthus, squill, apocynum and convallaria, have been shown to be inferior to digitalis in cardiac therapy. Therefore these preparations need not concern us further.

Too much emphasis cannot be laid on the two chief principles of digitalis therapy: the proper digitalization of a patient with auricular fibrillation and the maintenance of that digitalization.

Quinidin Therapy of Auricular Fibrillation.—Now we come to the other and more recent method for the treatment of auricular fibrillation, namely, by the administration of quinidin sulphate in the attempt to abolish this abnormal rhythm. For many years certain European physicians, on the Continent, particularly, had found that quinin combined with digitalis, or given alone, seemed to act beneficially at times on the heart, but no analysis was ever made of this beneficial effect. In 1914, Wenckebach reported that in two cases of auricular fibrillation he had succeeded in restoring normal rhythm by quinin. The first case which called his attention to the possibility of the use of the drug for this purpose was that of a Dutchman who had spent some time in the tropics, where he had acquired the habit of taking quinin for illnesses. He suffered from paroxysms of auricular fibrillation not controlled by his doctor. He discovered himself that when he took quinin for some complaint he secured relief from the paroxysms of auricular fibrillation. This discovery he reported to Wenckebach and Wenckebach was discerning enough to appreciate its significance. Following this finding various other alkaloids of cinchona bark were tried by Frey to determine their effect on auricular fibrillation. It was discovered in this way that quinidin sulphate acted much better than quinin or any of the other alkaloids from this bark in abolishing auricular fibrillation, and reports of clinical investigation with quinidin have become more and more frequent from all over the world. From one-half to two-thirds of all the patients with absolute irregularity of the pulse have had a restoration to normal rhythm, but in a certain considerable percentage of these cases fibrillation has recurred.

At the same time that quinidin sulphate was being introduced clinically Thomas Lewis was experimenting on the mechanism of auricular fibrillation and auricular flutter. He has shown in recent years by his work on animals and man that the mechanisms of auricular flutter and fibrillation are closely allied and that auricular fibrillation does not consist, as previously believed, in the simultaneous and dissociated activity of many different parts of the auricular musculature. Instead he has shown that auricular fibrillation is the result of a very rapid circus movement of a wave of contraction around the great veins. As has already been stated in the discussion of auricular flutter, the circus movement of auricular fibrillation travels at a faster speed than that of flutter. The action of quinidin is to put an end to this circus movement with a return of function of the normal pacemaker of the heart, namely, the sino-auricular node.

One of the aims of investigation has been to determine what type of case of auricular fibrillation is best treated with quinidin. Quinidin therapy, besides failing in a certain percentage of patients, also is not without danger, one source consisting of the production of embolism upon the reëstablishment of normal rhythm. In auricular fibrillation there

is a tendency to stagnation in the auricles; this stagnation sometimes results in thrombosis, particularly in the auricular appendages. Upon the resumption of a regular contraction of the auricles some of this thrombus may be pumped out into the circulation and result in embolism, which may kill the patient. Therefore, in the selection of cases of auricular fibrillation for quinidin therapy care should be exercised to pick out those patients in whom there is little likelihood of auricular thrombus. Such patients are those that have had auricular fibrillation for a relatively short time, that is for weeks or months, or at the most a year or two, those cases of fibrillation which have not had congestive failure of any appreciable degree past or present (for in cases with failure the circulation, being more sluggish, favors thrombus formation in the auricles), and finally those cases with auricular fibrillation without well-marked mitral stenosis (for in mitral stenosis there is apt to be auricular thrombosis). Fortunately the very cases in whom there is the least danger of embolism are the cases that respond best to quinidin sulphate in the restoration of normal rhythm and in the maintenance of this normal rhythm. One-third of all the cases of auricular fibrillation are favorably influenced by quinidin for a satisfactory length of time and these consist chiefly of patients with paroxysmal or recent auricular fibrillation without failure or mitral stenosis. It is of little avail to restore normal rhythm if within a day or two or a week or two there is a relapse to auricular fibrillation; the very patient in whom there is the most danger of embolism and who responds to the drug usually with more difficulty in the first place is more apt to relapse quickly. Another possibly important but unproved danger is from auricular standstill followed by standstill of the whole heart due to the toxic effect of quinidin at the moment of the abolition of the circus movement of auricular fibrillation.

There is then a definite place for quinidin therapy in the treatment of heart disease, but this treatment must be limited to the third of the group of patients with auricular fibrillation described above, possibly also to some cases with auricular flutter and paroxysmal tachycardia, and perhaps to some with premature beats.

Another danger with quinidin therapy that is easily averted and very unlikely to occur is due to individual idiosyncrasy to the drug. Rarely one meets patients who are hypersensitive to quinin; such patients are equally hypersensitive to quinidin. The toxic effects of quinidin are exactly those of quinin, ringing in the ears, nausea, headache, and, if extreme, respiratory paralysis. Rarely doses larger than 30 grains a day may be necessary.

A practical method for the administration of quinidin sulphate is as follows: On the first day test doses of 3 gr. (0.2 gm.) each are given at two or three-hour intervals, say at 2 P.M and 4 P.M. The drug may be given either in capsule or tablet form. I have had equally good results

with both methods. These initial small doses are given to test the sensitiveness of the individual to the drug. The following day, provided there has been no toxic effect from the quinidin, the administration begins in larger dosage: 6 gr. (0.4 gm.) are given every two hours for five doses, say at 8 and 10 A.M., 12 M., and 2 and 4 P.M. On each occasion, before the next dose is due the patient should be examined to determine whether or not there are toxic symptoms, or whether normal rhythm has been restored. If either condition is found, the drug should be discontinued for the rest of the day at any rate. These large doses of quinidin sulphate, that is, 2 gm. or 30 gr. a day, may be continued for several days even up to a week or ten days.[1] Sometimes four and five to six or eight days pass by before the pulse returns to normal. Most of the successful cases, however, are restored to normal within the first two or three days, and some of my cases at the Massachusetts General Hospital have returned to normal after one or two or three doses on the first day.

Finally, comes the question of the rationing of cases with quinidin after restoration of normal rhythm to prevent the occurrence of paroxysmal or permanent fibrillation. There is no doubt that quinidin sulphate in daily rations of 3, 6, 9 or 12 gr. (0.2 to 0.8 gm.) is effective in abolishing or diminishing in number, and shortening in duration, paroxysms of auricular fibrillation. There is, however, doubt as to whether it is wise to ration every case after restoration of normal rhythm. I believe one must experiment in individual cases. Some patients of mine have had normal rhythm now for several years or more and have not needed to take any quinidin since their auricular fibrillation was abolished. Other patients have relapsed and on the restoration to normal rhythm a second time have done better on daily rations. There does not seem to be any injurious effect from long-continued use of the quinidin daily in small doses, regarded as rations. The great subjective relief from the palpitation occasioned by auricular fibrillation in some patients is an important reason in itself for the use of quinidin.

HEART-BLOCK

Heart-block may be one of three types: sino-auricular, which has already been discussed under sinus arhythmia; auriculoventricular, which will be discussed in the present section; and intraventricular, which will also be discussed.

Auriculoventricular heart-block consists of retardation of the conduction of the stimulus for the heart beat from auricles to ventricles. It may be of any grade from the slightest delay in conduction, as shown electrocardiographically by a long P-R interval or on the jugular pulse tracing

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[1] In a few patients, after failure to control fibrillation, a second course of quinidin, with doses as high as 60 grains a day for a few days, has been given.

by a long *a-c* interval, up to complete heart-block with a slow ventricular rate of 25 to 30. The cause of the high-grade auriculoventricular heart-block is almost invariably arteriosclerosis of the coronaries; occasionally syphilis or rheumatic heart disease will be the factor.

Intraventricular block of all grades is, as a rule, of as much or more serious significance than is auriculoventricular heart-block. For its discovery the electrocardiogram is essential. It also is almost invariably produced by arteriosclerosis; rarely syphilis or rheumatism may be a factor.

The lesser grades of auriculoventricular heart-block, especially the slightest grades, are frequently produced in the clinic at large by digitalis, and in the study of the cause of heart-block in any given case great attention must be paid to the question of the quantity of digitalis administered and to the susceptibility of the individual patient to the drug. In this the study of the T wave of the electrocardiogram helps us a good deal, for the T wave is influenced by digitalis even sooner than the P-R interval, which is the conduction time between auricles and ventricles. If the T wave is flattened or inverted we may suspect, in a given case, that the digitalis administered is responsible for some of the block present. Very rarely can digitalis produce temporary intraventricular block.

With a high-grade auriculoventricular block, partial or complete, there tend to be in some patients spells of faintness or even syncope, and, if long continued, epileptiform convulsions. The association of such spells with heart-block is called the Adams-Stokes syndrome. The spell is nothing more nor less than a condition of cerebral anemia resulting from the temporary asystole of the heart due to the high-grade block.

Treatment.—The treatment of heart-block is of two types: first, etiological, and second, symptomatic. If we know the cause we should so far as possible try to remove it. For example, if we are quite sure that digitalis has produced the block we should omit the digitalis if there is not a clear indication for continuing the drug in the presence of congestive failure. If syphilis is found to be the cause of the block, antiluetic treatment is indicated, and occasionally cases have been seen and sometimes reported showing the striking cure of even high-grade heart-block under such conditions. But since arteriosclerosis is the cause in most patients who show well-marked auriculoventricular block and intraventricular block very little can be accomplished in the treatment of the cause. Until we can cure arteriosclerosis most cases of high grade heart-block, whether auriculoventricular or intraventricular, will resist all our attempts. However, some cases of high grade heart-block due to coronary disease spontaneously recover normal rhythm, apparently with the restoration of a better coronary circulation.

Symptomatically heart-block can be helped occasionally, but very rarely does heart-block produce symptoms. There may be coincident angina pectoris or congestive failure, but such conditions are not the result of the

heart-block and so do not enter into the present discussion. Rarely, as I have already said, high-grade auriculoventricular block may be associated with the Adams-Stokes syndrome, and in the treatment of a given attack of Adams-Stokes syndrome such drugs as depress vagal action or stimulate sympathetic action are indicated; for example, adrenalin, atropin sulphate, amyl nitrite inhalations, ammonia, caffein and other stimulants. Adrenalin chlorid, if necessary, injected directly into the heart is most effective under such conditions and it is worth while in emergencies. Often the attacks are so transient, however, that there is no time to give any remedy before the attack is over. To avert attacks various therapeutic measures have been devised. The occasional use of nitrites or of atropin or belladonna is unsuccessful in most cases. Thyroid extract in daily doses (gr. i to vi) seems to help in some cases and tends to maintain a higher ventricular rate and so to improve the circulation in patients with high-grade block, either partial or complete. Barium chlorid has also been used to stimulate ventricular activity and so to prevent the Adams-Stokes syndrome, in doses of ½ grain three or four times a day. For the greatest effect over short intervals of time—an hour or two, adrenalin (epinephrin), 10 to 15 minims of 1 : 1000 solution of the chlorid, subcutaneously, is most potent. Recently ephedrin, ½ grain orally three times daily, has been tried and recommended for the more permanent prevention of Adams-Stokes syndrome and probably is more effective than either barium chlorid or thyroid extract.

PULSUS ALTERNANS

Pulsus alternans is one of the most important and serious of all disorders of the heartbeat. It is a sign of an exhausted myocardium. It consists of regular alternation in force of the heart beats and can be detected, as a rule, only by examination of the arterial pulse, best either at the elbow by the use of the sphygmomanometer or at the wrist by the sphygmograph. Rarely can alternation be detected easily by the fingers palpating the radial pulse. If it is found in this way it is of high grade. The simplest method is that with the use of the sphygmomanometer. In such an examination it is discovered that alternate beats which occur perfectly regularly in time have a pressure from 2 to 3 up to 10, 20 or even 30 mm. below that of the preceding beats; that is, the pulse rate can be halved when the pressure in the cuff is raised to a certain level. The mechanism of the production of pulsus alternans consists probably in partial asystole of the heart muscle, that is, due to improper circulation or to intoxication or fatigue the refractory period of certain heart muscle fibers is prolonged to such a degree that they cannot contract with every stimulus. Therefore, during alternate heart beats some of the muscle fibers are lying idle recovering sufficient reserve to contract with every other stimulus.

Pulsus alternans is found particularly in patients who show hypertension and myocardial weakness. Hypertensive and arteriosclerotic heart disease are the conditions most often showing pulsus alternans. Occasionally any type of heart disease, however, will show the condition provided the heart muscle is weak enough. The presence of absolute arhythmia, in auricular fibrillation, prevents one from discovering the condition of the heart that would produce pulsus alternans, for, of course, pulsus alternans cannot be diagnosed when auricular fibrillation is present. Premature contractions, however, are often very helpful in revealing the presence of pulsus alternans, for following premature contractions there is a tendency for pulsus alternans to develop for a few beats in the borderline cases. Even this degree of alternation of the pulse is important and shows myocardial exhaustion.

Generally speaking, the finding of pulsus alternans entails a poor prognosis and most patients showing it have shortened lives. Usually the patient dies within a year or two of the discovery of the alternation. Rarely, with great care, a patient may live for even five or six years after the discovery of the condition.

There is one occasion when pulsus alternans is not of serious omen and that is during paroxysmal tachycardia, when after hours or days the heart muscle becomes fatigued and shows temporary alternation of the pulse.

Treatment.—The treatment of pulsus alternans consists simply in the treatment of the myocardial exhaustion. Rest is the first essential and usually absolute rest in bed with the head elevated is indicated for days, weeks or months so long as the myocardial exhaustion persists. Digitalis is indicated generally, and should be given at least a therapeutic trial in most cases. It used to be believed that digitalis was contra-indicated in pulsus alternans; this idea is no longer held by those who have investigated the condition. Jean Heitz and some of his associates have found that some of the patients who show pulsus alternans show also nitrogen retention in nephritis with hypertension. It is quite possible that poisoning resulting from renal insufficiency is a factor in a number of cases and the treatment of nephritis as well as the treatment of the cardiac weakness should be carried on.

CHAPTER XLVII

THE TREATMENT OF ADAMS-STOKES CONVULSIVE SYNCOPE OF HEART-BLOCK

George Herrmann

The necessity for and the advantages of a means of control of the asystolic attacks of heart-block are obvious. Such is offered by the use of barium chlorid. It must be realized that any attack may prove fatal, for it can never be foretold when the suspended ventricular contractions will or will not be resumed. When the ventricular standstill persists for more than five minutes, the prolonged anemia and resulting anoxemia of the brain tissues thereby induced, threaten irreparable changes in the vital nervous centers. Spontaneous ventricular ectopic beats or a series of contractions of the same origin, an irritable focus in the ventricle, serve to reëstablish the circulation. In recovery this source of the life-reviving or life-sustaining impulse becomes the ventricular pacemaker of an idio-ventricular rhythm. This rhythm is usually regular and slow, maintaining the circulation at the rate of about forty ventricular systoles per minute. As a rule the complete block persists and the relatively slow ventricular rate of contraction continues. There may be, however, a reversion from the idioventricular pacemaker back to the supraventricular source of the stimulating impulse. This is especially so in instances where the ventricular stoppage has resulted from the shift from partial heart-block to complete block with the ventricle failing to take up the secondary initiative rhythm. In rare instances there may be a sudden reëstablishment of the auriculoventricular conduction.

Barium and calcium salts were long ago proven, experimentally, to increase the irritability of the ventricular specialized tissue and heart muscle so that frequent contraction initiating stimuli arise, producing ectopic premature contractions. The ectopics were found to occur singly at first and then in shorter or longer runs of tachycardia (Rothberger and Winterberg).

It was later demonstrated that barium chlorid exerted the same influence even after complete traumatic auriculoventricular block (Von Egmond).

The drug thus has been shown to cause the onset and continuance of a rapid idioventricular rhythm (Junkmann).

BARIUM CHLORID

This drug presented itself as an ideal therapeutic agent (Cohn and Levine) in just such conditions as have been described as being present in Adams-Stokes' attacks of convulsive syncope in heart-block. The ventricular specialized tissue and muscle are apparently in a state of depressed irritability whenever a syncopal attack is precipitated. The presence of a constant minimum concentration of barium in the specialized tissue and the ventricular muscle seems to keep the idioventricular tissues irritable. Thus, when occasion demands, an idioventricular focus will assume the rôle of secondary pacemaker for the ventricles, initiating stimuli promptly, giving rise to beats and so preventing any periods of dangerously prolonged ventricular asystole with syncope, convulsion, and even fatal issue.

Barium chlorid, then, is, one may say, a prophylactic drug to be used continuously in the prevention of the occurrence of syncopal attacks of heart-block in any case in which the symptoms and signs of ventricular asystole have occurred. In cases where a complete relief from attacks is not accomplished, there is usually a shortening of the length of time of individual attacks or a decrease in the frequency of attacks. A rare case of absolute failure of the drug to act has been reported by Heard. This instance may have been due to the lack of absorption of the drug or to inadequate dosage for the given individual. Barium chlorid is relatively insoluble and at best is poorly absorbed from the gastro-intestinal canal. Thus far, however, no other methods of administration have been employed.

Preparation, Dosage, and Dangers of Barium Chlorid.—The crystals of barium chlorid may be conveniently put up for oral administration in small capsules containing 30 to 60 milligrams (½ to 1 grain). It is probably safer to use the 30 milligram (½ grain) capsule as the standard dose. This conservative dose of 30 milligrams may be given every three or two hours for a total of four or six doses, or 120 to 180 milligrams (2 to 3 grains) in twenty-four hours. As much as 300 milligrams (5 grains) have been given in a day for several days in succession without any noticeably harmful effect. In general, however, this must be considered an unnecessarily large dose and should be administered only in the most obstinate cases where the attacks of ventricular standstill continue even after twenty-four hours of the standard 30 milligram dosage. The dangers of larger doses lie in the possible production of ventricular tachycardia, ventricular flutter, and even ventricular fibrillation which in itself usually proves fatal. This latter disturbance, ventricular fibrillation, in attacks with accompanying convulsive syncope, has apparently been produced by barium chlorid in one of my patients who had complete heart-block, but who had had no syncopal attacks at least for many months preceding the use of barium chlorid. The attacks followed about half an hour after the administration of the drug. Barium chlorid is thus not entirely without

ill effects in the larger doses. A similar though less severe paroxysmal tachycardia appeared in a case of Strauss and Meyer.

The only indication for the use of barium chlorid is specifically the presence of Adams-Stokes' attacks of perceptible length or of moderate frequency. Neither partial nor complete heart-block should in itself, without symptoms or signs suggestive of ventricular standstill, be considered an indication for the use of the drug. This is true because the drug is purely an ectopic excitant and in no way does it improve conduction or relieve block. It should be used, so to speak, as a reserve or secondary powder cap to insure the setting off of a contraction when the usual impulse fails. In most instances the smaller and moderate doses might be tolerated without evident effect. Then again, as pointed out above, serious complicating cardiac mechanism disturbances may be induced. The possibility of such disturbances must be kept in mind and especially looked for when the drug is apparently not effective and when the dosage is being increased. Certain chemicals closely related to barium chlorid may have a similar beneficial effect. *Calcium lactate* in 1 gram (15 grains) doses, three times daily, has been accompanied by freedom from attack. *Strontium salts* have as yet not been tried and the relative values of the members of the alkaline earth group have not yet been studied.

THE EMERGENCY MANAGEMENT OF A SYNCOPAL EPISODE

In an acute attack of ventricular stoppage, barium chlorid as a specific emergency drug administered for the first time, is of no value. This is principally because it cannot be forwarded to the heart tissues promptly enough to bring about the resumption of ventricular activity. The direct injection of the drug into the heart or a jugular intravenous injection, has not been resorted to and must be considered dangerous. The drug when administered by mouth is relatively slowly absorbed and effects are rarely evident in less than half an hour and usually not for several hours.

Certain emergency methods must always be resorted to in every Adams-Stokes' attack, for one can never be certain that a given attack might not prove fatal. The patient must be kept at absolute rest in a horizontal position or in bed with the head lowered. Prompt and active reflex stimulation by briskly and forcefully slapping the precordium with the palm of the hand or even striking it with the clenched fist, sometimes serves to start up ventricular contractions again. This maneuver should always be tried. In the meantime, as the attack persists, speedy preparations should be made for more heroic measures. If the attacks happened to come on, as is sometimes the case, during an abdominal operation and if the abdomen is open, the surgeon should promptly resort to active massage of the heart through the diaphragm. In general, however, preparations for the injection of drugs, especially epinephrin, in 0.5 c.c. dose of 1:1000 solu-

tion directly into the heart must be made (Phear and Parkinson, Korns and Christie).

Epinephrin (adrenalin) is the traditional and still the most reliable emergency drug for cardiac stimulation, the drug of choice in ventricular standstill. Epinephrin promptly increases the irritability of the heart tissues through its stimulating action on the accelerator endings and probably through its depressing action on the vagus. The lowering of vagal tone and the stimulating of the accelerators often allows the conductivity of the auriculoventricular bundle to rise to the level at which auricular impulses pass to the ventricle again (Garrey, Meek and Eyster). This latter effect, however, is not always to be hoped for nor is it necessary to improvement. Epinephrin in only the rarest instances has been associated with serious complicating mechanism disturbances, such as ventricular fibrillation. It is, however, an ideal drug for administration under the desperate conditions of an Adams-Stokes' attack, for it may be administered directly into the heart by an extra long hypodermic needle. The intramuscular route is, as a rule, too slow and even the intravenous route fails to deliver the drug to the heart when there are no ventricular systoles and the venous return flow is impeded. The introduction of epinephrin into the jugular vein in the direction of the heart and the subsequent placing of the patient in an upright full Fowler's position in the hope that by gravitation the drug may reach the heart, may be tried. In any extreme situation, however, the only sure method of administration is the injection of 0.5 c.c. of a 1:1000 solution directly into the heart through a long fine needle. The intracardiac instillation is heroic but practical. The effects of epinephrin are unfortunately transitory, but the recurrence of attacks has been prevented by the frequent repetition of injections. Frequently 0.5 c.c. of a 1:1000 solution of epinephrin hydrochlorid will ward off attacks for several hours. The intradermal injection of the drug with rubbing of the site of injection at hourly intervals will greatly prolong the beneficial effects of epinephrin. Attacks have been interrupted and suspended indefinitely by the use of as little as two injections of epinephrin a day for ten days.

Ephedrin has more recently come into favor as a substitute for epinephrin in most of the conditions in which the latter drug has proven effective (Stecher). Adams-Stokes' disease has been no exception to this rule. Ephedrin is not as prompt nor as potent in its action as is epinephrin, but it is more sustained in its effects and has the distinct advantage of being effective even when administered by mouth. Ephedrin can, however, also be given by needle and can be combined with epinephrin in half dosage of each with gratifying results. Ephedrin hydrochlorid is given in 30 to 60 milligram (½ to 1 grain) doses three times daily and gradually decreased to the lower dosage twice daily.

Thyroxin in 1 milligram (1/65 grain) doses given intravenously or

intracardiacally has a stimulating effect upon cardiac tissues, increasing the irritability as epinephrin does. Thyroxin has in its favor the fact that it is not known to have produced ventricular fibrillation as epinephrin has experimentally done in the heart of the dog and is thought to have done in rare instances in the human heart.

Atropin has produced paradoxical effects, depending upon which of its effects is predominating the auricular rate increase, or the accelerator stimulation, or the vagus paralyzing effect. Where an increased vagus tone plays a great part in the production of the heart-block as is commonly the case, spectacular results accompany the vagus paralysis with atropin. In the rarer type of case with more organic and functional damage in the auriculoventricular conduction tissues, the increased auricular rate or a prolongation of the refractory period of the auricular and specialized conduction tissue act as the last straw, and suddenly increase the block to completeness, and often also precipitate syncopal attacks. Atropin sulphate to be effective is given in 1.3 to 2 milligrams (1/50 to 1/30 grain) doses subcutaneously or even intravenously. *Novatropin* is fifty times less toxic and consequently can be used in much greater dosage with correspondingly more atropin effect and at the same time less danger.

Digitalis not infrequently produces heart-block which may even progress to complete dissociation, but characteristically the idioventricular rate of this type of heart-block is high, usually in the neighborhood of sixty beats per minute and sometimes even higher. Digitalis increases the rhythm of the ventricle and digitalis block is most rarely associated with ventricular standstill. Adams-Stokes syndrome is, however, not infrequently precipitated by the inability of the idioventricular pacemaker to initiate an impulse with the suspension of the impulse from the auricle in the transition from partial to complete auriculoventricular heart-block. In such cases it is safer to digitalize the patient and to establish and maintain complete heart-block.

SUMMARY AND CONCLUSIONS

Each case of Adams-Stokes convulsive syncope in heart-block is an individual therapeutic problem in itself. During each attack of ventricular standstill the emergency measures must be resorted to. After the circulation is reëstablished, immediate steps should be taken to prevent the recurrence of these attacks. It is in this prophylactic rôle that *barium chlorid* is most useful. It has been experimentally proven to increase the excitability, irritability and spontaneity of the specialized ventricular tissues and to insure idioventricular impulses with resulting ventricular contractions. In rare instances barium chlorid may fail and in any case in which it has been given in adequate dosage for two days, other means of increasing cardiac irritability should be tried. Whenever the attacks are particu-

larly frequent or tend to be prolonged, no matter what other drug is being used, I believe that supplementary treatment with small doses of epinephrin intradermally should be instituted to tide the patient over the critical period.

Barium chlorid should be regularly administered in a dose of about 30 milligrams daily for months after a series of attacks. I have had a patient continue on 50 milligrams each morning for two years without any detrimental effect and without the recurrence of anything that simulated an Adams-Stokes syndrome. I believe the regular daily ration of the drug is preferable to the intermittent use or course of barium chlorid. The course idea is likely to prove dangerous, principally because the patient is apt to become careless and to neglect his treatment in a false sense of security, in which he had managed to get along without medicine for a time and will most probably continue likewise. If, however, he is impressed with the fact that freedom from attacks and even his life is dependent upon the daily maintenance of a constant minimum concentration of the drug in his heart-muscle, he is more likely to coöperate conscientiously. It is necessary to keep his ventricular focus irritable and ready to respond whenever it is called upon to do so. Potassium salts, because of their depressing effect upon the heart-muscle, should not be used in the treatment of any chronic syphilitic condition in the presence of heart-block.

Since this article was written further reports emphasizing the possible toxic effects of barium chlorid have appeared. T. M. McMillan and C. C. Wolferth (*J. Lab. & Clin. M.,* St. Louis, 1929, 13 : 829) reported an untoward effect of barium chlorid in producing short runs of aberrant ventricular beats in doses of 20 milligrams four times a day. The same dose twice daily was tolerated well and had prevented syncopal attacks for many months. Each increase in the number of doses precipitated paroxysms which were recorded in this carefully studied case. S. P. Schwartz (*Am. Heart J.,* St. Louis, 1929, 4 : 612) announced toxic manifestations of barium chlorid after the administration of two doses of 30 milligrams with a four hour interval. The drug was tried only once. The case was unsuitable because of the electrocardiographic findings which should have indicated to the author the presence of widespread serious myocardial damage. Furthermore, there was no indication for the drug in this case in that the patient had never had syncopal attacks. These cases, however, further emphasize the care that must be exercised in the use of barium chlorid.

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CHAPTER XLVIII

THE SURGICAL TREATMENT OF DISEASES OF THE HEART AND PERICARDIUM

C. S. Beck and E. C. Cutler

The special field of cardiac surgery [1] includes the treatment of wounds of the heart, the treatment of pericardial effusions, and the treatment of cardiopericardial adhesions. In addition to these, there exists a large group of valvular conditions that primarily are abnormalities in the dynamics of the circulation. As such this group of cardiac conditions should be amenable to a mechanical form of therapy and within recent years this group of disorders has made a special appeal to the surgeon.

MITRAL STENOSIS

It is with some trepidation that the subject of relieving certain valvular disorders by surgery is presented because the results up to the present time are unsatisfactory. Justification in presenting the subject, however, may be found in the belief that the future holds promise of helping certain of these cases by operation.

The first time that the human heart was operated upon was in 1895, when Cappelen sutured a wound. At that time this operation was considered one of the boldest steps the surgeon had ever taken. Three years later an English veterinarian, Samways, said "that with the progress of cardiac surgery some of the severest cases of mitral stenosis will be relieved by slightly notching the mitral orifice." At about the same time Arbuthnot Lane, an English physician, tried to select a case that would be satisfactory for the procedure. In 1902 Sir Lauder Brunton stated that "the good results that have been obtained by surgical treatment of wounds of the heart emboldens one to hope that before long similar good results may be obtained in cases of mitral stenosis." Sir James Mackenzie gave the proposal careful consideration, but felt that he "would rather leave the troubles and the dangers for others."

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[1] For a more detailed discussion of the subject the reader is referred to the articles by Matas in *Keen's Surgery*, Vols. 5 and 7, and by Cutler and Beck in *Nelson's Loose-Leaf Surgery*, Vol. 4.

RATIONALE OF THE PROCEDURE

It is an accepted fact that the heart can make a better adaptation to mitral insufficiency than it can to mitral stenosis. Patients with mitral insufficiency may live to an old age, but patients with mitral stenosis usually die early. To excise a piece of the stenosed ring would decrease the obstruction but at the same time it would increase the leak. Could the function of the heart be improved by such a change in the mechanics of the circulation?

The medical literature gives comparatively little help in answer to this question. The only definite evidence in its support is the fact that the heart makes a better adaptation to a mitral leak than it does to a mitral obstruction. This evidence is of importance, but before attempting to relieve the mitral obstruction in the human heart, the question should be settled, if possible, by experimentation. Many experiments were carried out, the purpose of which was first to produce mitral stenosis and later to relieve the stenosis by operation, but it has been impossible to produce mitral stenosis in animals. To throw light upon the question, experiments in which the animal was sacrificed were carried out. Pressures in the various chambers of the heart were determined after placing a stenosing ligature at the mitral valve and also after relieving the ligature and producing an accompanying regurgitation. These determinations, however, have no application to the problem, because the conditions produced were not compatible with life and the adaptability of the heart to them could not be determined.

With the failure to produce mitral stenosis in animals the basic idea remains undemonstrated. Are patients suffering from mitral stenosis, therefore, justifiably subjected to operation for its relief? After considerable investigation and experiment the question was answered in the affirmative by Cutler who subsequently performed the first operation upon a patient with mitral stenosis.

TECHNICAL METHODS

Numerous methods for the exposure of the heart have been described, in which were utilized incisions made in the midline parallel to the sternum, incisions made in various directions to the left or to the right of the sternum, and osteoplastic flaps in which one or more ribs were reflected.

Median Sternotomy.—The skin incision extends from the level of the second interspace to the midpoint between the umbilicus and the xiphoid (Fig. 1). The xiphoid may be either removed or separated on one side from its ligaments and aponeuroses. The underlying structures are freed from the sternum, and a spatula is inserted beneath it to protect the heart.

The sternum is split longitudinally with a saw or bone shear to the level of the second or third intercostal space, where it is cut across, care being taken to avoid the internal mammary vessels. The sternum is retracted, and the pleuræ are dissected laterally with a moist sponge. The peritoneum
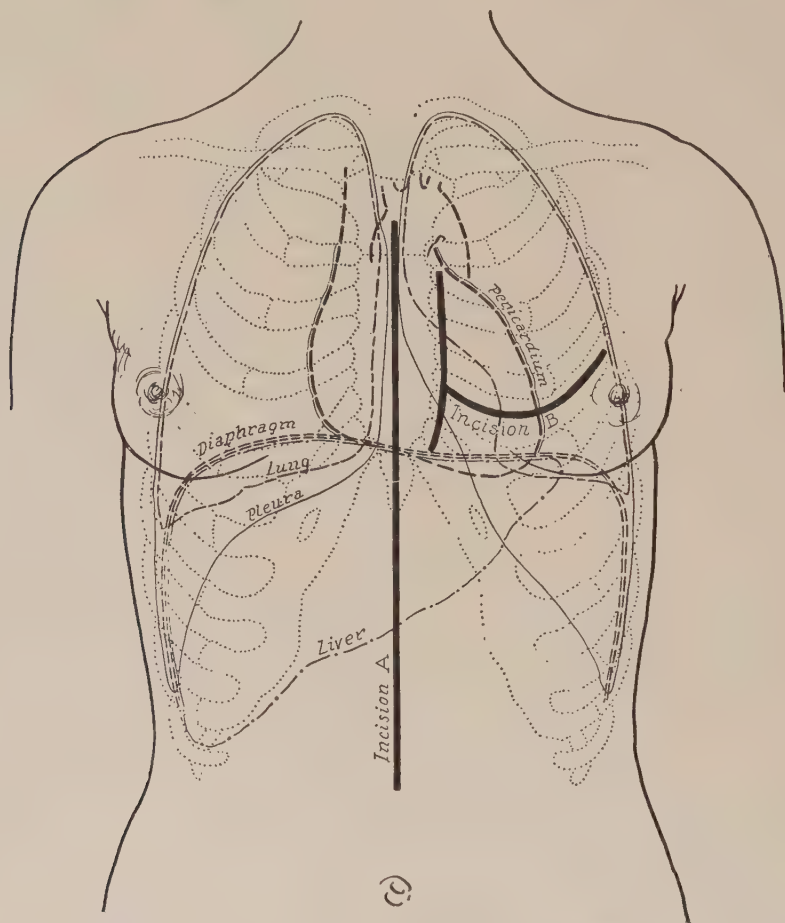
Fig. 1.—Outline Drawing of the Chest Showing the Placement of Incisions for Exposure of the Heart and Pericardium.

Incision A is the median sternotomy. Incision B is the intercostochondral thoracotomy. (E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

is opened and the anterior portion of the diaphragm is incised. The pericardium is opened widely, the incision extending to its reflection on the diaphragm. An excellent exposure of the heart is obtained (Fig. 2). The structures are closed in layers. The sternum should be securely approximated with several silver wire sutures that encircle it. This procedure provides the most extensive exposure of the heart. It has in its favor also

the fact that the pleura is not opened. It is, however, an extensive operation and during the postoperative period the respiratory movements may
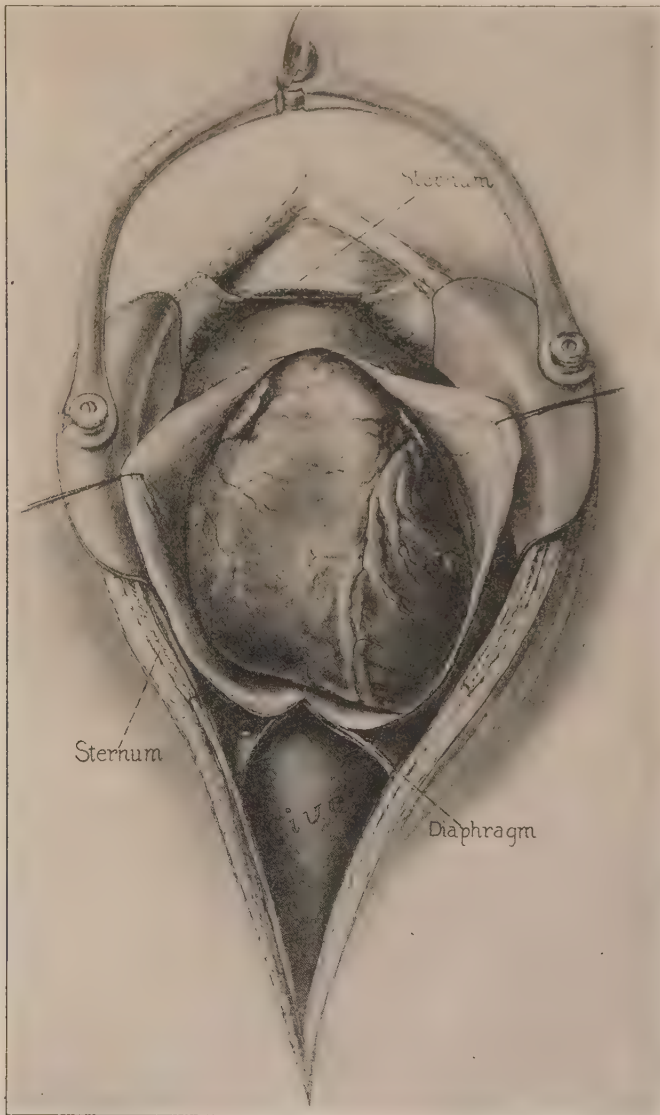
FIG. 2.—EXPOSURE OF THE HEART BY THE MEDIAN STERNOTOMY.

be accompanied by considerable pain. This exposure was used by the writers in six cases of mitral stenosis (Duval and Barasty, Milton).

Intercostochondral Thoracotomy.—The incision is made in the left fourth intercostal space extending from the anterior axillary line to the

sternum, where it is continued in each direction along the margin of the
sternum to expose the third, fourth, fifth and sixth costal cartilages
(Fig. 1). These costal cartilages are sectioned; the internal mammary
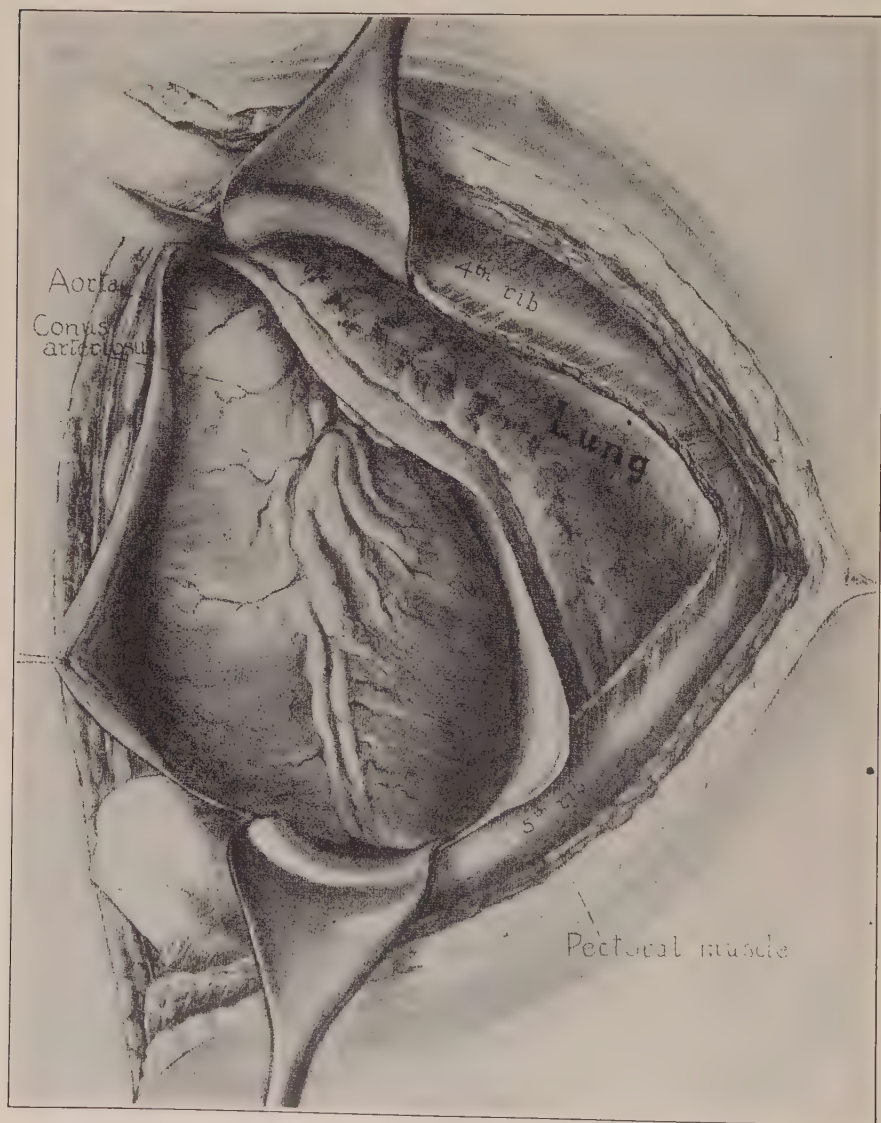
FIG. 3.—EXPOSURE OF THE HEART BY THE INTERCOSTOCHONDRAL THORACOTOMY.

vessels are ligated, and the incision is extended through the underlying
muscles into the pleura. The structures are retracted and the pericardium
is opened. The left lung, the left ventricle, and part of the right ventricle
are exposed (Fig. 3). Part of the right ventricle and the base of the

heart, including the auricles, are not exposed. To increase the exposure of the heart it has been suggested that the second costal cartilage be divided and that the sternum be split transversely (Spangaro, Durante, Wilms).

Excision of Costal Cartilages.—If the method of approach to the mitral valve does not necessitate a full exposure of the heart, as is the
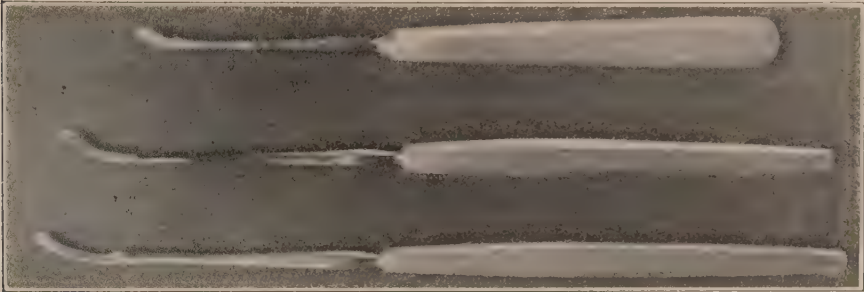
FIG. 4.—KNIVES USED BY CUTLER TO CUT THE MITRAL VALVE.

case with the auricular approach, a much less extensive thoracotomy may be utilized. The pericardium is exposed by removal of the third, fourth, fifth and sixth costal cartilages on the left. The adjacent portion of the sternum also may be removed. The pleura need not be opened if its extension anteriorly is dissected from the mediastinum. When the pericardium
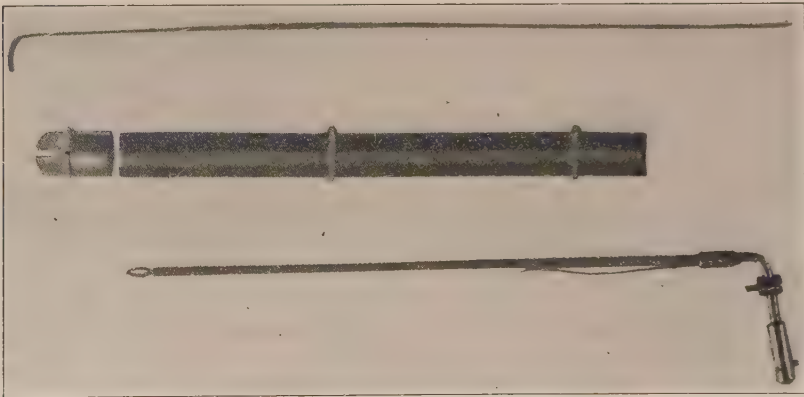
FIG. 5.—CARDIOSCOPE OF ALLEN AND GRAHAM.

is opened a fairly wide exposure of the left auricle is obtained, but little if any exposure of the ventricles is provided. The authors used this method in one case of mitral stenosis.

Methods of Enlarging the Stenotic Orifice.—Various methods have been utilized for the enlargement of the mitral orifice. Tuffier and Souttar attempted to dilate the constricted orifice with the finger. Doyen and

Cutler used small tenotome knives for incision of the mitral valve (Fig. 4). Allen and Graham, realizing the difficulty of orientation within the heart, devised a cardioscope which provided a small degree of vision and which carried a small knife to cut the valve (Fig. 5). Because of the difficulty encountered in incising a thickened, calcareous valve, Beck and Cutler devised an instrument, the cardiovalvulotome, by means of which a piece of valve can be excised and removed from the blood stream
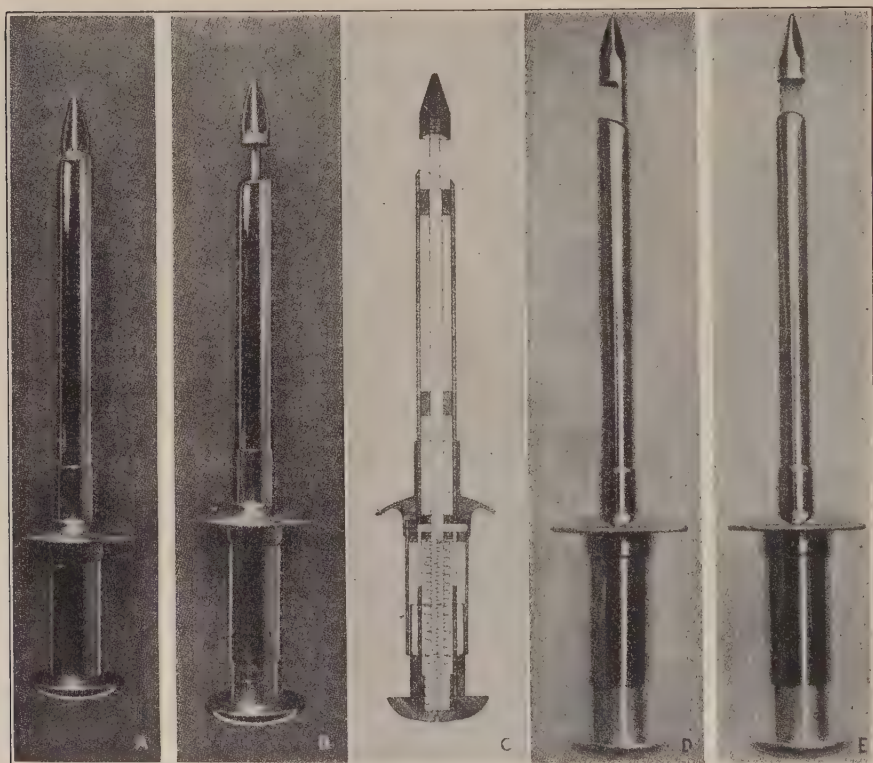
FIG. 6.—CARDIOVALVULOTOMES OF BECK AND CUTLER.

Utilizing the shearing principle the instrument can cut the toughest valve. The excised segment is encased in the instrument and removed from the blood stream.

(Fig. 6). To this instrument a visual apparatus has been added, but the degree of vision afforded has helped but little in orientation within the heart.

Method of Approach to the Valve.—The mitral valve may be approached through the auricle or through the ventricle. If the ventricular approach is used, it is necessary to expose the heart by the midsternal route. If the auricular approach is used, the heart may be exposed by a less extensive parasternal incision. It is a moot question as to which of these methods is preferable. With either the ventricular or auricular
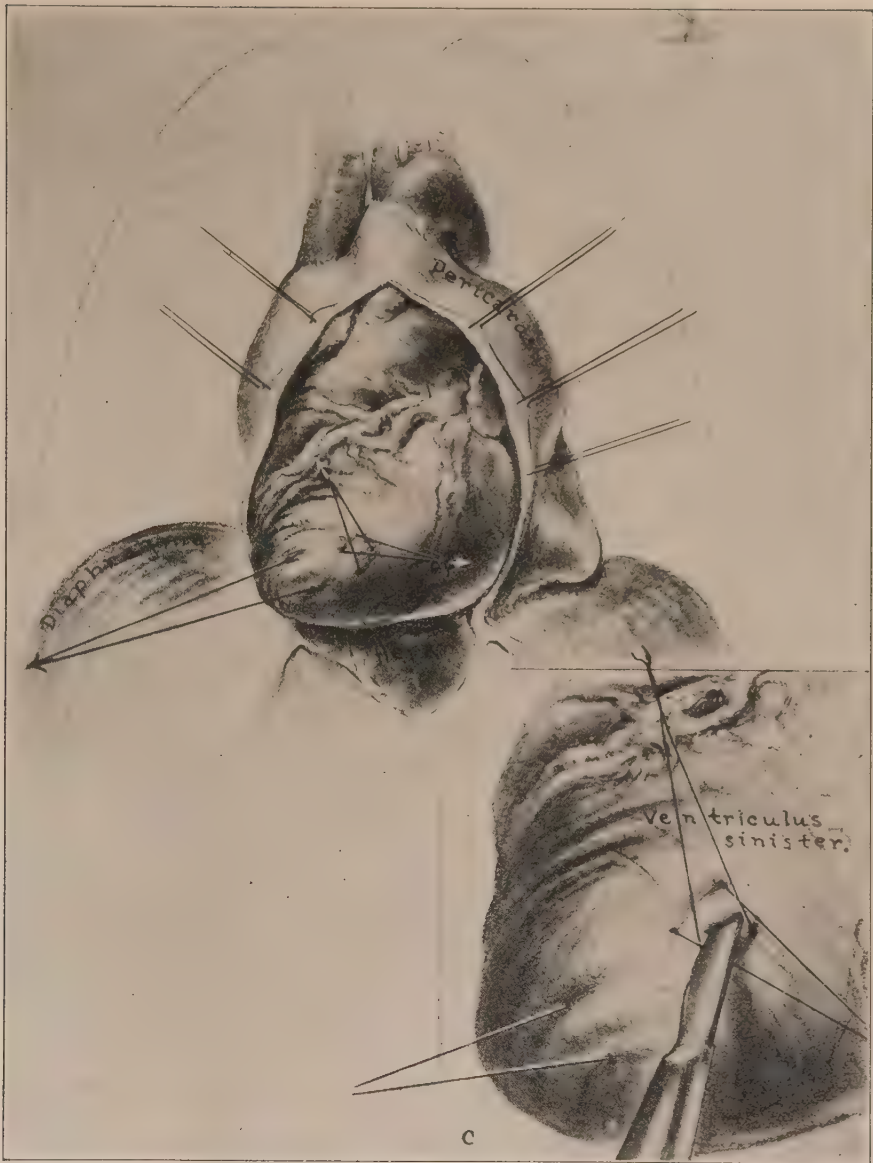
Fig. 7.—The Heart Is Handled by Means of a Suture Placed in the Apex. Sutures to Control Bleeding Are Placed before the Incision Is Made.

(E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

approach the possibility of hemorrhage is a question of technic, and in either case it can be completely obviated. The auricular route carries with it the possibility of dislodging a thrombus from the auricle. Access to the mitral valve is less difficult through the auricle than by way of the
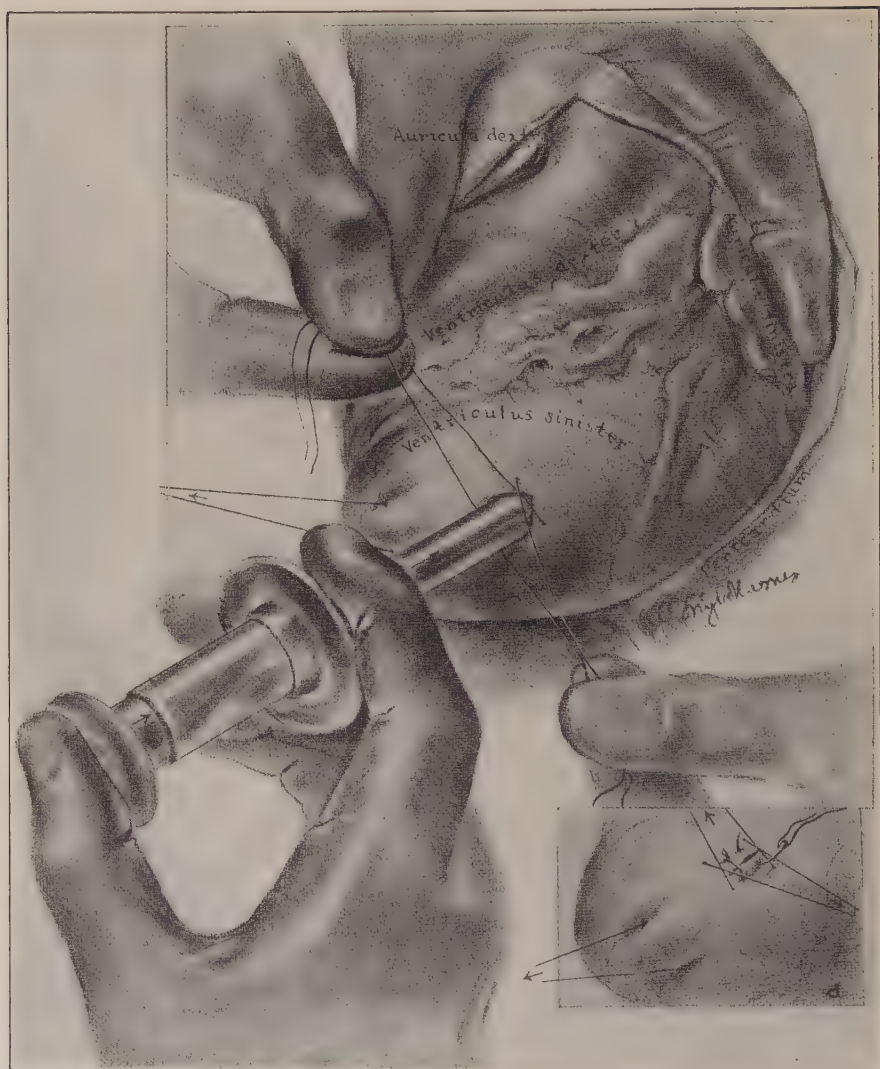
Fig. 8.—The Cardiovalvulotome Is Inserted into the Heart and the Index Finger
Placed over the Auricle Feels the End of the Instrument in the Region
of the Mitral Valve. The Inset Shows the Sutured Wound.

(E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose
Leaf Surgery,* Thomas Nelson & Sons, New York.)

ventricle because the auricle slopes into the mitral valve in the form of a
cone.

Ventricular Approach.—If the ventricular approach is used, a suture
for handling the heart is placed in the apex; this apex suture is very im-
portant (Fig. 7). A region devoid of coronary vessels, as near the apex
as possible, and away from the base of the anterior papillary muscle, is

selected for the introduction of the knife or the cardiovalvulotome. Two sutures of silk taking a deep bite of muscle are placed in the area selected for the insertion of the instrument so that the four threads represent on the surface of the heart a square of 1 centimeter. A small scalpel is placed between these sutures and the ventricular wall is cut in a plane slightly oblique to the surface of the heart. If there is any bleeding, the sutures which have been crossed are made slightly taut. The cardiovalvulotome,

FIG. 9.—SKETCH OF THE CARDIOVALVULOTOME IN THE LEFT VENTRICLE.

The portion of the stenosed mitral valve to be excised is indicated by the dotted line. (E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

after having been filled with salt solution to displace the contained air, is introduced through the incision into the cavity of the left ventricle and is then allowed to open (Fig. 8). The cutting edges are introduced into the mitral ring, the position being determined by the index finger of the left hand, as it feels the end of the instrument through the invaginated wall of the left auricle (Fig. 9). The mitral valve now lies between the cutting edges, and by telescoping the handle a portion of it is excised and encased in the instrument which is then removed from the heart. Slight traction upon the sutures prevents any bleeding as the instrument is withdrawn, and the wound is closed with one or two silk sutures.

Auricular Approach.—The auricle can be entered most safely through its appendage. A purse-string suture is placed around the base of the auricular ear to control bleeding. The tip of the appendix is excised and through this opening the knife or cardiovalvulotome can be inserted. After withdrawing the instrument the opening in the auricle is closed either by suture of the opening or by ligature of the base of the auricular appendage.
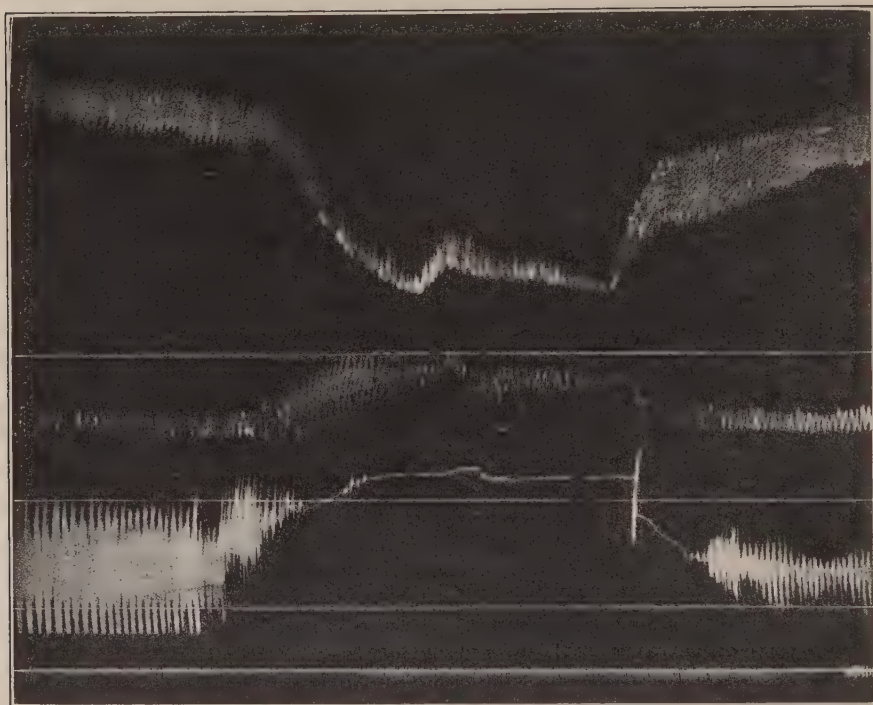
Fig. 10.—Effect of Cardiac Tamponade.

The upper curve shows arterial pressure, femoral; middle curve, venous pressure, innominate, and lower curve, intrapericardial pressure. The intrapericardial pressure was increased 10 centimeters of water and caused a marked fall in the arterial pressure and a rise in the venous pressure; on release of the intrapericardial pressure the arterial and venous pressures returned to their former levels. The time is shown in seconds.

Cardiac Tamponade.—The development of cardiac tamponade is a very serious postoperative complication, and in one of our cases of mitral stenosis it proved fatal. For its detection roentgenograms of the heart should be taken daily during the postoperative period. If fluid collects in the pericardium, it should be evacuated either by aspiration or by opening the wound.

The mechanism of cardiac tamponade is shown in the accompanying graph (Fig. 10). To avoid it the pericardium should be left open for 1 or

Résumé of Case Reports

Case	Author or Operator	Date	Diagnosis	Method or Instrument	Result
1..	Cutler and Levine	May 20, 1923	Mitral stenosis	Tenotome	Died 4½ years after operation
2..	Allen and Graham	Aug. 7, 1923	Mitral stenosis	Cardioscope	Operative death
3..	Cutler, Levine and Beck	Oct. 7, 1923	Mitral stenosis	Tenotome	Died 10 hours after operation
4..	Cutler, Levine and Beck	Jan. 12, 1924	Mitral stenosis	Tenotome	Died 20 hours after operation
5..	Cutler, Levine and Beck	Feb. 25, 1924	Mitral stenosis	Cardiovalvulotome	Died 6th day after operation
6..	Cutler, Levine and Beck	June 11, 1924	Mitral stenosis	Cardiovalvulotome	Died 3rd day after operation
7..	Souttar	May 6, 1925	Mitral stenosis and aortic insufficiency	Finger dilatation	Recovery—living and improved
8..	Pribram	Nov. 14, 1925	Mitral stenosis and aortic vegetative endocarditis	Cardiovalvulotome	Died 6th day after operation
9..	Cutler and Beck	Dec. 8, 1926	Mitral stenosis	Cardiovalvulotome	Died 15 hours after operation
10..	Cutler and Beck	Apr. 15, 1928	Mitral stenosis	Cardiovalvulotome	Died 3 hours after operation

2 centimeters so that fluid, if it forms, may escape into the wound. Drains should not be placed into the pericardium because their presence leads to the formation of adhesions (Beck and Moore).

Summary of Cases.—Of the ten patients with mitral stenosis that were operated upon, one survived, giving a mortality of 90 per cent. Eight of the ten patients died so soon after operation that the changes brought about in the dynamics of the circulation could not be adequately studied. One patient lived four and a half years after the operation. It is difficult to say definitely whether in this case the enlargement effected in the mitral valve was followed by an improvement in the circulation. If it be true that the mechanics of the circulation were improved by reduction of the stenosis, a definite advance in this subject has been brought about. It will require, however, a number of cases successfully operated upon to determine definitely whether an improvement in the circulation can be expected by enlarging the orifice of the stenosed valve. Such physiological observations have not been produced experimentally, and it seems that the basic idea underlying the development of this subject will have to be established by attempts upon human patients.

Problems.—If it is granted that reduction of the stenosis improves the dynamics of the circulation, there remain the technical problems of the operation. That the procedure can be carried out without loss of blood and that the heart can tolerate section of the stenosed mitral valve has

been demonstrated. To reduce the hazards of the operation a number of problems must be settled.

Of greatest importance is the problem of localization of the mitral orifice in relation to the instrument which sections the stenosed valve. An operative procedure to be successful should be carried out under the guidance of vision. To clamp off the base of the heart, to lay open the ventricle, to incise the mitral valve and finally to suture the wound in the heart is an ordeal that cannot be tolerated. It has been found experimentally that the heart and the brain can tolerate ischemia for a limited period of time. This period of safety in the dog was one and one-half minutes (Rehn); in the cat, three minutes (Cutler, Levine and Beck); and in the rabbit, three and three-quarters minutes (Laewen and Sievers). If the obstruction was continued beyond these limited periods, either the heart failed to recover its normal rhythm or signs of degeneration of the cortical cells developed subsequently. The human heart, undoubtedly, can tolerate this procedure better than the heart of lower animals, but under the most favorable circumstances the time that could be taken would be insufficient to carry out the procedure with any degree of equanimity. The flow of blood through the heart, therefore, cannot be interrupted during the procedure. This limitation of method necessitates adequate instruments to be inserted into the heart to cut the mitral valve.

The brilliant results afforded by cystoscopy suggested naturally the application of a similar visual method to the heart. The urologist is well aware of the handicap of a cloudy fluid medium, and, of course, in the opaque medium of blood the light in the cystoscope is completely deadened. With modifications of the visual apparatus, however, a more or less imperfect degree of vision can be obtained in the heart. The lamp should not come into contact with the blood. The objective should be a planoconvex lens of short focus. A seat to contain the lamp should be ground in the lens to avoid reflection of light. When direct contact with the lens is established, valve leaflets, chordæ tendineæ, and endocardium can be recognized. It was felt, however, that the results of cardioscopy were too imperfect to justify the added complexity of the procedure which it entailed.

The type of exposure of the heart and the approach to the valve also constitute important aspects of the technical procedure. The midsternal approach was used in seven of the ten cases operated upon. It is an extensive operation in itself, probably too extensive to warrant its use. In one case an osteoplastic flap was turned back and the pleura opened. In two cases a less extensive exposure of the heart was obtained by resection of costal cartilages with or without resection of a portion of the sternum. After having utilized the midline sternotomy and the ventricular approach to the valve in six cases, we adopted in our seventh case (Case 10 of the summary) the less radical exposure by resection of costal cartilages and

sternum and the approach to the mitral valve through the auricle. It was our hope that the auricle might furnish a more exact approach to the mitral valve.

From the above summary of cases it is seen that three kinds of procedures were utilized in the attempt to enlarge the stenotic orifice. These methods were dilatation by finger, incision of the stenotic valve and excision of a segment of the valve. We have had no experience with dilatation of the stenosis, but we feel that the method may be worthy of trial. Incision of the stenotic valves was carried out in four cases. In two of them the enlargement effected by incision was inadequate, and the conclusion was reached that excision of a segment of the mitral valve was necessary if the obstruction was to be relieved.

The adaptability of the heart immediately after the stenosis has been reduced merits comment. There is both clinical and experimental evidence to indicate that the enlargement of the mitral orifice must be relatively slight. Otherwise pulmonary congestion and cardiac failure develop. We feel that the enlargement should not be greater than half a square centimeter. It would be preferable if the stenosis could be transformed into an insufficiency by a gradual process.

STENOSIS OF OTHER VALVES

The first intracardiac operation was for the relief of stenosis of the pulmonary valve. In this case Doyen, in 1913, inserted a small tenotome knife into the right ventricle, and attempted to cut the stenosis. The patient died a few hours after the operation, and at necropsy there was found a congenital narrowing of the conus arteriosus and its associated anomaly a perforation of the interventricular septum. The second case was by Tuffier, in 1914, for the relief of aortic stenosis. Dilatation was attempted by inserting the finger into the stenosis through the invaginated wall of the aorta. Ten years after the operation the patient was reported to be living and improved.

PATENT DUCTUS ARTERIOSUS

Of the many congenital abnormalities of the heart the only one that seems to offer promise to surgery is the uncomplicated patent ductus arteriosus. In this condition blood flows from the aorta where the pressure is relatively high into the pulmonary artery where the pressure is lower. A part of the oxygenated blood in the aorta is returned to the lungs and there is thus set up a short-circuit. The heart is placed under a distinct handicap, and it seems reasonable to assume that if the communication were ligated, the heart would be relieved of this handicap. The operation was suggested by John Munro, in 1907, but according to the literature it

has never been carried out. Usually the patent ductus arteriosus is associated with other cardiac abnormalities. Since these associated abnormalities are usually compensatory, ligation of the ductus arteriosus should not be carried out in such cases.

TRAUMA

The history of wounds of the heart forms a fascinating chapter of medical literature. The heart being a vital organ, wounds of it were considered uniformly fatal. The first successful attempt to suture a wound of the human heart was carried out by Rehn in 1896. Since that time several hundred cases have been collected in the literature. Since the advent of suture the mortality of wounds of the heart has dropped from 85 per cent to about 30 per cent.

The diagnosis of a wound of the heart is comparatively easy, especially if the mechanism of cardiac tamponade is held in mind. When the heart is wounded blood collects in the pericardium and cardiac tamponade is produced. The pulse becomes rapid and faint, the blood-pressure falls and the patient may become unconscious. The site of the injury may be of assistance in the diagnosis but in some of the recorded cases the wound of entrance was far distant from the precordium. If there is a large rent in the pericardium the patient may succumb quickly from exsanguination into the thorax. The area of cardiac dulness even in the presence of tamponade may not be increased demonstrably. This is due to the fact that only a comparatively small amount of blood can be contained in the pericardium when the bleeding occurs suddenly and also to the fact that the size of the heart itself is decreased because of the compression. The roentgenogram is of little help in the diagnosis.

Treatment.—The treatment of wounds of the heart is clearly established. All cases of wounds of the heart that show cardiac tamponade should be operated upon immediately. Those that do not show signs of hemorrhage or compression may be treated conservatively. A foreign body in the heart, as a needle or a file, should be removed cautiously. If the foreign body is large so that hemorrhage may follow its removal, the foreign body should not be removed until the heart has been exposed at operation so that the wound may be sutured. The exposure of the heart should be carried out either by the Duval-Barasty or by the Spangaro exposure (Figs. 2 and 3). The latter should be used if there is an associated wound of the lung from which there is active bleeding.

Several methods have been proposed for the suture of the wound of the heart. Sauerbruch, in 1907, described a method by which the wound can be sutured, while the base of the heart is compressed between the fingers. The accompanying illustration (Fig. 11) describes the method in sufficient detail. The objection to this method is that the flow of blood through the coronary arteries and through the brain is stopped during
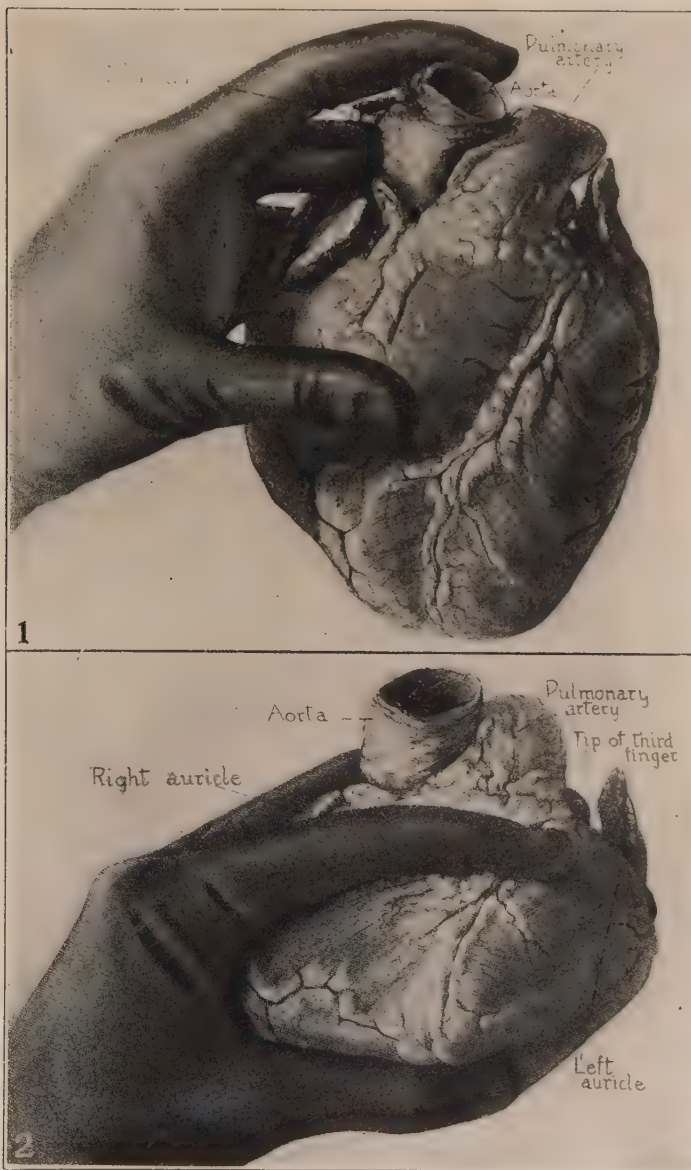
FIG. 11.—METHOD FOR THE SUTURE OF WOUNDS OF THE HEART (SAUERBRUCH).

The upper drawing shows the third finger placed through the great transverse sinus and the fourth and fifth fingers are posterior in the pericardial cavity. By compression with the fingers the venæ cavæ and pulmonary veins can be occluded. The lower drawing shows the heart steadied between the thumb and index finger so that the wound can be sutured.
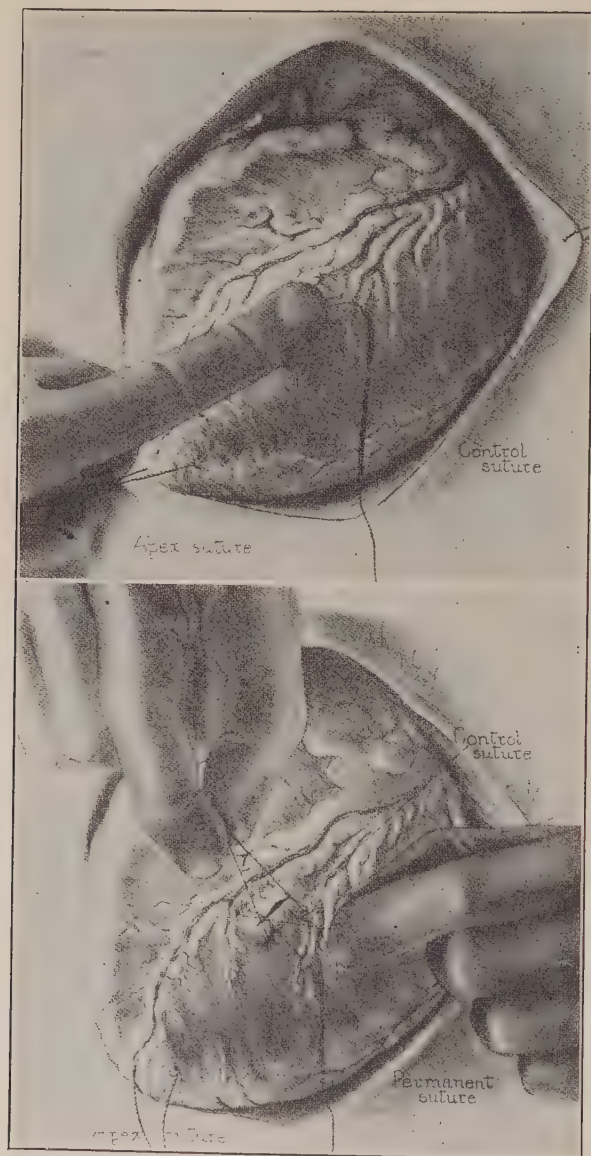
FIG. 12.—METHOD FOR THE SUTURE OF WOUNDS OF THE HEART (BECK).
A suture to steady the heart is placed in the apex. The index finger is placed over the wound to stop the bleeding. Two control sutures are then placed on each side of the finger. The control sutures are crossed, the finger removed and the wound exposed. The wound can then be sutured carefully without bleeding.

the period when pressure is exerted on the great veins at the base of the heart, and this can be tolerated for only a very short space of time.

Another method (Fig. 12), recently described by Beck, is free from

the danger of anoxemia to the heart and to the cortical brain cells. As soon as the pericardium is opened a suture to steady the heart is placed in the apex, the wound in the heart being momentarily disregarded. The apex suture is held under traction between the thumb and the third finger of the left hand, and the index finger is placed on the wound. The bleeding is thus controlled. While the index finger is thus maintained upon the wound, two control sutures taking a deep bite of muscle are placed, one on each side of the finger at the level of the wound. They are crossed and then held under gentle traction by the assistant, as the index finger is removed. The apex suture is dropped. An excellent exposure of the controlled wound is provided and ample time may be taken in placing the permanent sutures. Coronary vessels, if they lie adjacent to the wound, can be avoided in the sutures, and a neat approximation can be obtained. The apex and the control sutures are removed.

PERICARDITIS

Diseases of the pericardium are frequently unrecognized by the physician. According to the statistics of Locke, only 17 per cent of 150 cases of acute pericarditis at the Boston City Hospital were diagnosed clinically. This is extremely unfortunate because surgery can accomplish much in the therapy of this condition. Similarly cases of adhesive pericarditis are too infrequently given the benefit of surgical therapy.

Paracentesis Pericardii vs. Pericardiostomy in the Treatment of Sterile Effusions

The effusion should be removed from the pericardium in all cases in which the fluid impairs the cardiac function. How the fluid should be removed in cases of sterile effusion, whether by aspiration or by incision and drainage, has become a question of argument. The accidents that have accompanied aspiration of the pericardium have led some writers to oppose strongly the procedure of aspiration and to advocate the operation of pericardiostomy. One such fatality has come under our experience and the literature contains a number of fatalities from aspiration. There are, however, clinicians of extensive experience who have aspirated the pericardium many times without a serious accident; judging from this experience it may be drastic to lay aside the aspirating needle for the scalpel and ribshear.

If aspiration of the pericardium is carried out, it should be done only with a consciousness of its possible danger. The observation of the movement of the heart transmitted through the aspirating needle with no apparent ill effect is no just cause for the internist to marvel at the wonders of nature. In every case in which aspiration of the peri-
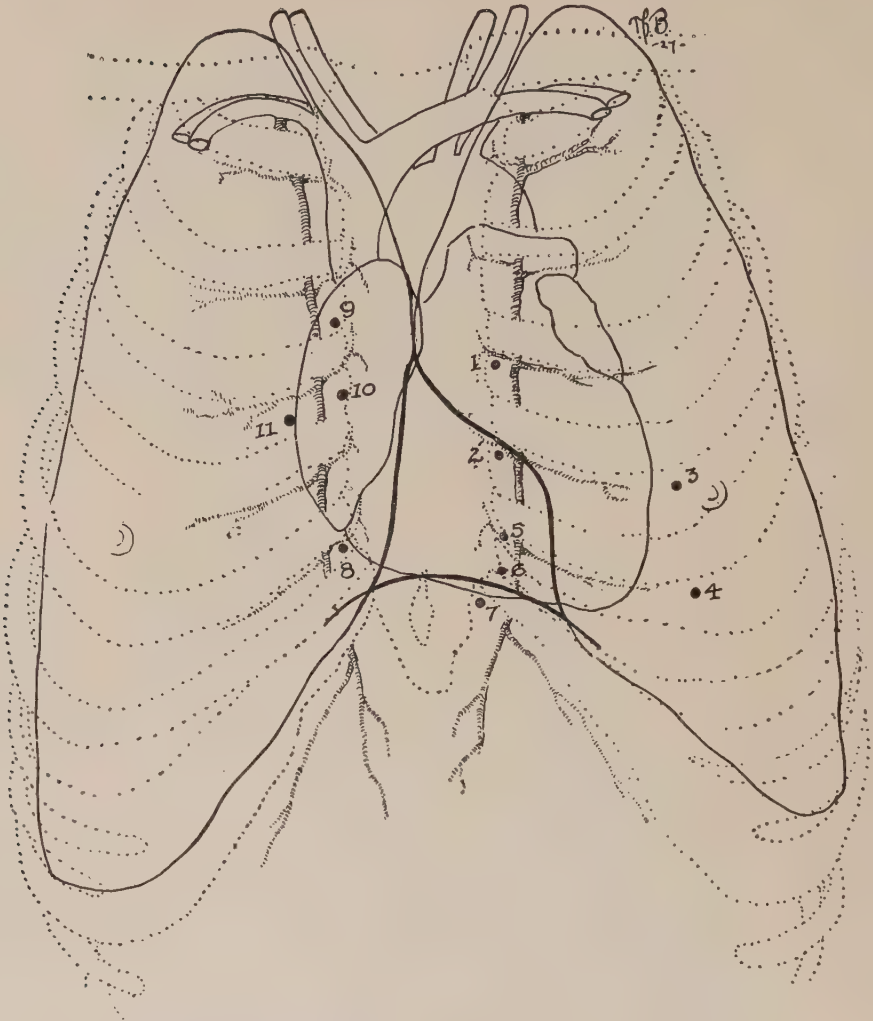
FIG. 13.—POINTS OF ELECTION FOR TAPPING THE PERICARDIUM.

1. Schuh, Sharp; 2. Trousseau; 3 and 4. Dieulafoy; 5. Baizeau; 6. Delorme and Mignon, Hare, Voinitch-Sianojentzky; 7. Larrey, Pendlebury, Allingham and Roberts; 8. Rotch, Wilson, Schapochnikoff; 9, 10, 11. Other points used. The area bounded by heavy lines is the "triangle of safety." Aspiration within this area has the advantage of avoiding the pleura. To avoid the pleura, therefore, points 2, 5, 6, 7 should be selected. (E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery,* Thomas Nelson & Sons, New York.)

cardium is carried out, the danger of cardiac tamponade should be held in mind; if it should occur, its development should be noted as early as possible so that the heart can be exposed at operation and the bleeding point sutured before death occurs.

There is some diversity of opinion as to the best site for aspiration

of the pericardium. The points of election as advocated by various writers are indicated in Figure 13.

The considerations that led to this diversity of opinion are the advisability (1) of avoiding the pleura and (2) of entering a spacious recess or cul-de-sac of the pericardium without injury to the heart, the coronary vessels and the internal mammary vessels.

The Treatment of Purulent Effusions in the Pericardium

All purulent effusions should be treated by pericardiostomy, and this operation should be carried out without delay after the diagnosis is made. The good results following evacuation of pus from the pericardium make
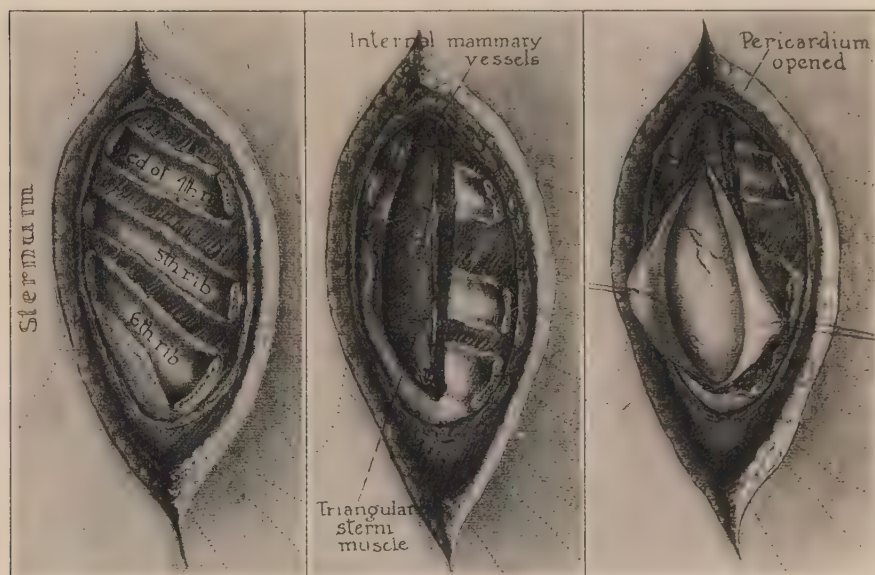
FIG. 14.—SUCCESSIVE STEPS IN THE OPERATION OF PERICARDIOSTOMY.
(E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

it incumbent upon the physician to diagnose the condition early so that the patient can be given the benefit of this therapy.

The operation of pericardiostomy can be carried out under local anesthesia. It is not an extensive procedure nor does it require any special skill. The operation is illustrated in Figure 14.

If the effusion is tuberculous the wound should be closed after the contents of the pericardial sac have been evacuated. If the wound be left open secondary infection may be superimposed upon the tuberculous process. If the tuberculous effusion is not too thick it may be removed by aspiration.

Adhesive Pericarditis

Chronic adhesive pericarditis is usually the result of the acute fibrinous form and usually occurs years after the onset of the disease. The most frequent predisposing causes are rheumatic fever and tuberculosis. The varieties of the disease are: (1) Adhesions limited only to a portion of the pericardium; (2) complete obliteration of the pericardial cavity;

Fig. 15.—The Operation of Cardiolysis (Brauer).
(E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

(3) obliteration of the pericardial cavity with extension into the surrounding structures, pleura, mediastinum and thoracic wall. In this condition the movements of the heart may be limited much as the movements of a hand are limited by a tightly fitting glove. At each retraction the heart pulls upon its harness of adhesions. Considerable effort is wasted upon the unyielding ribs and diaphragm. A further handicap to the circulation may be produced by constriction of the venæ cavæ or by adhesions distorting the arch of the aorta.

That certain cases of adhesive pericarditis can be helped by surgical intervention has been clearly demonstrated. These cases are (1) those in

which the heart is encased in scar tissue, and (2) those cases in which there are extensive adhesions between the heart, chest and diaphragm. The operation for the former condition, known as decortication of the heart, was suggested by Delorme, Beck and Rehn, and the operation was first performed by Rehn. The operation for the second condition, known as cardiolysis, was suggested by Brauer.
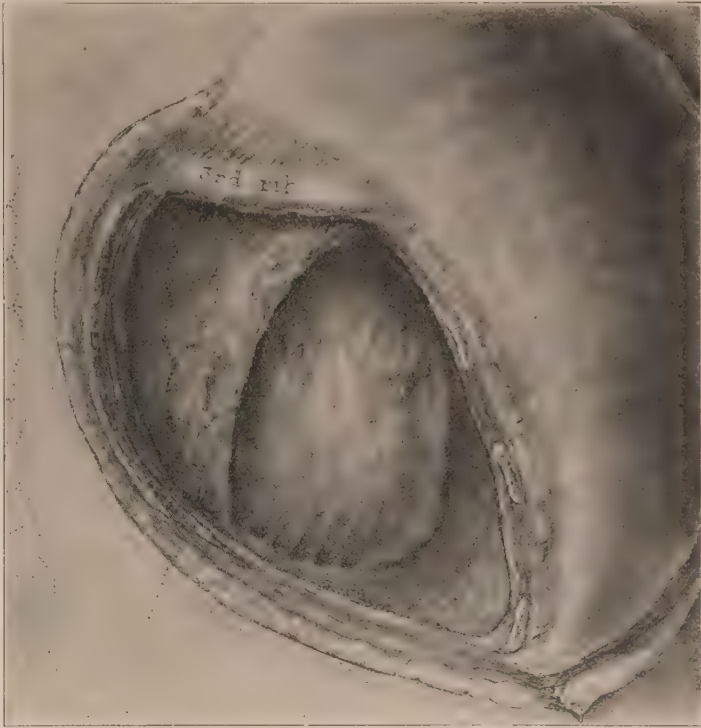
FIG. 16.—THE OPERATION OF DECORTICATION OF THE HEART.
(E. C. Cutler and C. S. Beck, "Surgery of the Heart and Pericardium," *Nelson Loose Loose Leaf Surgery*, Thomas Nelson & Sons, New York.)

Cardiolysis.—This ingenious operation consists of the removal of the rigid framework of the thoracic wall upon which the heart expends part of its force (Fig. 15). So simple is the execution and so good is the result that it is remarkable that this operation has not been given greater application than it has. In general, portions of the fourth, fifth and sixth ribs are removed and sometimes the third. If the heart tugs upon the sternum a portion of the sternum should be removed. The precordium is thereby transformed into a soft yielding structure which offers less resistance to the movements of the heart. Possibly the chief reason for the infrequent application of such an extremely satisfactory and simple operation lies in the difficulty in the diagnosis.

Decortication of the Heart.—This operation consists of the removal of the thickened and adherent pericardium from the heart (Fig. 16). The adherent pericardium may be so infiltrated with scar tissue that it can be removed only by sharp dissection. Frequently the scar formation invades the myocardium so that a definite line of demarcation does not exist. Emphasis is placed upon the fact that removal of the parietal layer alone is not sufficient but that the epicardium itself must be removed. Von Schmieden emphasizes the danger of freeing the right ventricle first because the ventricle, accustomed to its encasement, may dilate acutely and tricuspid insufficiency may develop and prove fatal. No attempt is made to decorticate the auricles. If the costal cartilages of the precordium have been removed at a previous operation, the soft parts of the anterior thoracic wall are sutured over the defect in the pericardium. Von Schmieden performed the operation on seven patients, and claimed that five showed definite improvement. At the present time we feel that there are insufficient data to justify definite statements concerning the value of this operation. We recommend, however, that the operation should be performed more frequently. The technical difficulties of the operation are such that it should be carried out only by a very careful operator. The operation is performed in successive stages. At the first operation the bony framework over the precordium is removed. Several months later after the heart has adapted itself to the thoracoplasty, the second stage of decortication of the left ventricle is carried out. Whether the dissection can be extended to the right ventricle at this stage depends upon the condition of the heart. An intervening period of rest may be advisable before the right ventricle is freed of its encasement. The soft parts are sutured in place and an adequate opening should be provided in the soft parts to allow the escape of fluid to prevent cardiac tamponade.

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CHAPTER XLIX

HYPOTENSION

Alfred Friedlander

Definition.—Low blood-pressure is not a disease. It is, in many instances, part and parcel of a diseased bodily state. But it is established that distinct hypotension is at times compatible with perfect health. It is also true that many hypotensive subjects possess great bodily vigor. It, therefore, becomes a matter of interest to discuss the various types of low blood-pressure, to determine their relation to various involved processes, and to establish, where possible, etiological relations between the hypotension itself and the diseases of which it is a manifestation. Various authors have tried to fix upon a single cause to explain diverse types of hypotension. This cannot be done. The interrelationship of the factors maintaining blood-pressure is always close and at times the connections are devious and hard to trace. For certain types of hypotension no adequate explanation has yet been found. The relation of the endocrine system to types of hypotension is an instance in point. In the syndrome known as "essential hypotension," it has yet to be proved that the low blood-pressure is the cause of all the symptoms.

For clinical purposes, the estimation of the blood-pressure by the auscultatory method, using a mercury manometer, is the method of choice.

Hypotension in Healthy Persons.—It is generally held that the normal limits of blood-pressure in healthy individuals are not fixed. The majority of writers, however, place the upper limit of the systolic pressure in hypotension at 110 millimeters in adults. It would appear that racial, environmental and climatic conditions may change the normal average of blood-pressure in young adults.

Thus the studies of Cadbury, Foster and others have shown that the blood-pressures of Chinese adults is lower by 10 to 20 millimeters than the pressures of normal Occidentals.

Tung showed that several years' residence in Pekin caused a marked drop in the blood-pressures of two-thirds of healthy Americans studied. Roddes and Cooper also call attention to the lowered pressures of the natives of the tropics. They found, furthermore, that prolonged residence in the tropics caused a gradual drop in the pressures of healthy foreigners. The change is not rapid and is probably to be accounted for on the basis of lowered vasomotor tone and general slowing of physiologic activity.

Statistical studies on large groups of healthy adults have shown that low blood-pressure is quite common, being found in 2.5 to 3.5 per cent of all persons examined. Friedlander's study of a series of large groups of life insurance risks revealed the fact that hypotension in healthy adults is not only common, but that, in the opinion of the insurance medical experts, the low blood-pressure adds to, rather than detracts from the normal life expectancies. The medical director of one company had tabulated the records of 3,389 persons (ages sixteen to sixty) accepted for insurance, who had systolic pressures of 100 millimeters Hg. or less. In the series there had been, up to the time of publication, twenty-six deaths, just 35 per cent of the expected mortality (American Men Table). The company's general mortality experience is about 80 per cent of that in the table. Hypotension also shows familial tendencies at times. Thus Garvin reported six cases in one family. All of these persons were in excellent health, none had systolic pressure over 102 millimeters, two were under 100. Most of these persons were robust, hypersthenic; one was obese.

Factors Entering into the Maintenance of Blood-Pressure.—It is generally believed that the variations of pressure found in certain percentage groups of apparently healthy persons are due to causes not clearly ascertained as yet. Some observers think that heredity, producing fixed though aberrant types of cardiovascular or vasomotor mechanisms, or combinations of both, may be a factor. It is certain that no single cause can explain the various clinical types of hypotension. Any discussion of such types of hypotension must concern itself with the consideration of those factors which maintain normal blood-pressure. These factors are:

1. The force of the cardiac contraction, the *vis a tergo*.
2. The condition of the vessel walls.
3. The peripheral resistance to the blood stream, determined by the vasomotor system.
4. The blood volume, and the physical state of the blood itself, its viscosity, etc.

These factors are *not* of equal importance. A weakened myocardium causes definite types of hypotension. The physical state of the conducting vascular system probably plays little rôle, except in certain forms of temporary hypotension. The factor of peripheral resistance is probably the most important single factor, both in the maintenance of normal pressure and in the production of hypotension. The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or depressor action on vasomotor function. Endocrine dysfunction, therefore, plays a definite rôle in the production of hypotension. The factor of peripheral resistance presents many phases, some of them deviously interrelated. The interpretation of hypotension associated with changed peripheral resistance causes us the greatest difficulties.

Change in blood volume and in blood viscosity is of considerable importance in the interpretation of certain types of acute hypotension (as in certain of the acute infections and in shock).

Types of Hypotension.— Low blood-pressure may be either a temporary or a persistent phenomenon. Acute hypotension is part and parcel of traumatic, anaphylactic, surgical and anesthetic shock. It occurs in certain of the acute infectious diseases. It may be the result of drug intoxication. Persistent hypotension occurs in association with certain chronic infectious diseases and cachectic states. It is found in such diatheses as status lymphaticus, infantilism, and myxedema. Lesions of the circulatory system, particularly of the myocardium, may produce either temporary or persistent hypotension. Certain types of body habitus are associated with low blood-pressure. Essential hypotension constitutes a fairly definite syndrome, the exact nature of which is as yet not definitely understood. Chronic hypotension may be due to abnormal vasomotor tone, due to changed condition of the capillary circulation. It occurs in conditions of endocrine gland dysfunction, especially of the adrenals, hypophysis, thyroid and gonads.

A (necessarily condensed) discussion of these types of hypotension follows.

TEMPORARY HYPOTENSION

Anaphylactic Shock.— Clinical studies, supplemented by experimental investigation, have shown that the low blood-pressure in anaphylaxis is due to dilatation and congestion of the large venous trunks of the splanchnic area, with coincident medullary anemia. The splanchnic congestion produces a lack of vasomotor tone with reduction in the blood volume. This change in blood volume tends to increase the drop in blood-pressure. The heart shows no initial changes.

Traumatic Shock.—The factors entering into the production of wound shock may be divided into initiating and sustaining factors, accounting, respectively, for primary and secondary shock. Primary shock is of much less importance than secondary shock. It is probably to be accounted for on the basis of a disturbance of the nervous system, with reflex dilatation of the blood-vessels. In secondary shock the cardiac factor is not of prime importance. Neither is exhaustion of the vasomotor center. The theory of shock best supported by clinical evidence and experimental study is that of a toxic factor, operating to cause an increased permeability of the capillary walls, and a consequent reduction of blood volume by escape of plasma into the tissues. Cannon adds that it is recognized that after sufficient time has elapsed, infection may occur and be of such a character in itself as to induce persistent hypotension. The work of Dale and Laidlaw, and Dale and Richards with reference to the drop in blood-pressure following the injection of extremely minute amounts of histamin

into animals, is of particular significance, with reference to the hypotension of traumatic shock. Although absolute proof is still lacking, there are many reasons for thinking that a substance, histamin-like in character, is given off when the tissues are severely damaged. There is strong reason to believe that the toxic factor in the production of wound shock is either histamin or some histamin-like body.

Hemorrhage is, of course, an added factor of importance in the direct reduction of the blood volume. In addition, cold, exposure and anesthesia after hemorrhage may be factors in the production of the hypotension. So, too, may be the marked relaxation of the capillaries, and injury to the capillary endothelium.

Surgical Shock.—Among the factors tending to favor the occurrence of surgical shock, may be mentioned hemorrhage, toxic agents from infection, loss of body fluids from various causes, tissue trauma, handling of the abdominal viscera, and the anesthesia itself. The diminution of blood volume in circulation during and after operation is the most potent factor in the production of the low blood-pressure which accompanies surgical shock. Moderate hemorrhage alone does not necessarily produce shock. Experimentally it has been shown that reduction in blood volume from hemorrhage exceeding 30 per cent causes a marked drop in blood-pressure. The fall in blood-pressure usually precedes the advent of shock symptoms by an appreciable interval. The so-called McKesson law is generally considered reliable: A pulse rate of 100 and ascending, with progressively falling blood-pressure reaching 80 or less (the so-called critical level), and a pulse pressure of 20 millimeters or less, if continued over thirty minutes, invariably ends in shock. Various other mathematical formulæ have also been worked out (Moots).

Blood-Pressure and the Anesthetic Itself.—All anesthetics in common use cause a fall in the blood-pressure, if the administration be continued more than a few minutes. Chloroform causes the earliest and most abrupt fall. The drop under ether comes later and is less marked. Nitrous oxid causes very little drop in pressure, unless administration be prolonged over two hours. Ethylene produces even more gradual changes in pulse, respiration and blood-pressure than nitrous oxid. It is not as depressive as ether. Spinal anesthesia is contra-indicated in operations in persons suffering from shock, for it produces a very marked drop in blood-pressure, particularly in the early minutes of its induction. Adams warns emphatically against its use in any operations on hypotensives. Epinephrin, given intravenously, is often of value in marked hypotension after spinal anesthesia.

Treatment of Traumatic and Surgical Shock.—The most important measure, in addition to external heat, rest, and sedatives, is to increase the blood volume. The simplest way to do this would be to give fluids by mouth or by rectum. Shock patients, as a rule, cannot retain fluids so given.

During the war it was found that transfusion is the best method for increasing blood-volume. English surgeons advocated the use of gum solutions, but accumulated experience has shown that they are not free from danger. There is no question of the value of blood transfusions in shock. Blood is probably preferable to any indifferent fluid. Simple salines are often of value, even if given subcutaneously. Of late, excellent results have been reported from the use of dextrose solutions, or of dextrose and insulin. Wade, as a result of his studies, says that the use of dextrose intravenously, with insulin subcutaneously, gives excellent results. Cases of traumatic shock treated early respond most readily to this treatment; cases of surgical shock show marked improvement. The optimal dosage he gives as 1000 c.c. of 5 or 10 per cent dextrose with one unit of insulin to 3 grams of dextrose. He thinks that cases where the blood-pressure is falling to the critical level should be treated immediately by this method.

HYPOTENSION IN ACUTE INFECTIOUS DISEASES

Most of the acute infectious fevers are accompanied by a fall in blood-pressure, in varying degree. In general terms the extent of the fall varies directly with the degree of fever, though there are definite exceptions to this rule. The type of infection, the general condition of the patient antecedent to the infection, and the fact that in some instances the pressure is influenced more by the toxemia than by the pyrexia, all militate against the working of the rule.

During the height of fever, blood-flow, especially in the capillaries, is slower than in health. Such relative capillary stasis would be a factor in the production of febrile hypotension. Newburgh and Laurence have shown that in lower animals, experimentally induced hyperthemia of degrees not greater than those encountered in infections, is sufficient to produce marked hypotension. Clinically, it may be said that the increased body temperature in infection is one factor in the hypotension which occurs. The weakened heart action, due to the cloudy swelling or degeneration of the heart muscle in certain of the acute infections, is another factor: the *vis a tergo* is weakened. In convalescence from prolonged fevers there is often a loss of splanchnic tone, due in part to nervous influence (toxemia), in part to weakened arterial musculature. This tends to lower blood-pressure still further. When the patient assumes the erect posture, the decreased cerebral supply must be compensated for by increased heart rate, and this throws an added strain on the heart.

It is thus apparent that various factors enter into the hypotension of the acute infections. The actual figures of blood-pressure are of less importance than the course of the pressure curve, upward or downward. Lability of pressure, with marked changes in pulse pressure, is of importance.

Typhoid Fever.—Apart from certain complications, the course of the blood-pressure is progressively downward. Rolleston believes that the hypotension is in direct relation to the severity of the attack. With the advent of hemorrhage, the pressure usually drops very sharply. Such a drop is to be explained by the diminution of blood volume. A sudden rise in pressure is sometimes found when perforation has occurred. It was formerly believed that such a rise was of importance as a diagnostic sign of perforation, but it is too inconstant. In association with other findings it may have confirmatory value. In order that blood-pressure changes in typhoid may have diagnostic value, daily readings must be made. Rolleston has found transient rises due to complicating pleurisy and cholecystitis.

Involvement of the myocardium is, of course, extremely common in typhoid. The cardiac factor is thus of prime importance in the causation of the hypotension. The vasomotor factor also plays a rôle (toxic vasomotor depression).

Pneumonia.—Hypotension is the rule in pneumonia, but it is by no means always present, even in the severest cases. The hypotension is due to the toxemia, and its effect on the vasomotor centers. Repeatedly attention has been called to the fact that death in pneumonia is attended by the symptoms and signs of surgical shock. The degree of toxicity in a given case may be rated by the severity of the "shock" symptoms during life. The condition of the heart muscle is a factor in the production of hypotension in some cases of pneumonia. The recognition of this cardiac factor has led to the widespread use of routine digitalization in the treatment of pneumonia.

Hypotension in pneumonia is due to a cardiac factor, a toxic vasomotor depression factor, or to a combination of both of these.

Influenza.—Hypotension is the rule during the acute stage of influenza. The asthenia during the last pandemic reached very extreme degrees. The cardiac factor, the vasomotor factor, and the reduction in blood volume all play rôles. The persistence of hypotension for a long time after the subsidence of the acute attack is due, in many instances, to myocardial involvement. Persistent lack of vasomotor tone also accounts for some of long continued postinfluenzal asthenias.

Diphtheria.—Marked hypotension is found in the most severe cases. Here there is reduction in blood volume due to uneven distribution of the blood. Vasomotor depression and myocardial involvement are also factors to be considered in some cases.

Malaria.—Hypotension is more common in chronic malarial cachexias than in acute forms. Clinically and experimentally, it has been shown that heavy infection may result in plugging of the capillaries with plasmodia, particularly the cerebral capillaries. Marked hypotension in chronic malaria may then have a certain prognostic value.

Cholera.—In the algid stage there is usually marked hypotension with diminished pulse pressure. The low blood-pressure is due to direct reduction in blood volume, due to loss of plasma from the circulating blood. The viscosity of the blood is also increased. The use of intravenous saline injections, whose value has been repeatedly attested clinically, tends to restore the blood volume.

Trichinosis.—Recent studies have shown that severe infestation with trichinæ usually produces marked hypotension. This is, in all probability, of toxic myocardial origin.

HYPOTENSION IN CHRONIC DISEASES

Tuberculosis.—In the advanced stage of the disease with pronounced toxemia, marked hypotension is the rule. In the incipient stage, however, there is no constant hypotension. Various investigators have found that the degree of hypotension stands in direct relation to the severity of the disease. The hypotension in tuberculosis is probably the result of a toxic action in the vasomotor center. Cardiac degeneration or atrophy is a secondary factor. In a recent review of the subject Stivelman adds that patients with fibroid phthisis usually show higher pressures than do those with other forms. The incidence of hemoptysis is greater in patients with low pressures, but there is no etiological relation. This author concludes that blood-pressure readings in tuberculous patients are not of prognostic value, but his studies showed that patients with pressures higher than the average for the whole group did better than the very low pressure cases.

Syphilis.—Recent studies have shown that there is nothing characteristic in the blood-pressure readings in the majority of cases of cardiovascular syphilis. Hypotension, when it does occur early, is in all probability dependent upon the factor of myocardial degeneration. Warthin has shown that in the early stages of syphilis there occurs an interstitial myocarditis, characterized by infiltration with lymphocytes and plasma cells along the vessels between the muscle fibers. A form of syphilitic hypotension to which attention has been paid of late is syphilitic lesion of the adrenals. Recent studies have shown that in a majority of the cases of autopsies in syphilitic persons, adrenal lesions are present.

Addison's Disease.—Marked hypotension is one of the outstanding clinical features of Addison's disease, although, as has been shown recently, it is not invariably present. Pathologically the principal lesion is tuberculosis of the adrenals. Syphilitic lesions of the adrenals have been found in a few instances. A considerable proportion of persons having Addison's disease show the characteristic features of the lymphatic or thymolymphatic constitution. It is, however, quite impossible to explain, completely, the hypotension of the disease in terms of dysfunction of one or of several of the factors which ordinarily maintain normal blood-pressure.

Organotherapy has been tried for over twenty-five years in the treatment of Addison's disease without very good results. Recently, the combination of forced substitution organotherapy, whole gland, with the addition of epinephrin, has been made the subject of special study.

Bronchial Asthma.—There is general agreement to-day that the underlying factor of primary bronchial asthma is protein sensitization of the individual. It is thus possible that the anaphylactic shock in asthma is due to a toxic split protein which, circulating in the blood, affects the autonomic nervous system. It is believed by some that imbalance of the endocrine system may also play a rôle. The hypotension is thus due to lack of vasomotor tone.

Focal Infections.—Focal infections arising from chronic inflammation of tonsils, teeth, accessory nasal sinuses, gall-bladder, genitalia, etc., are very frequently accompanied by marked hypotension. It is even asserted that the most persistent types of hypotension, belonging to the infectious group, occur in cases of focal infection. The low blood-pressure may even be a sign of diagnostic value. Such hypotension is due to marked depression of vasomotor tone, though myocardial change may also be of importance. It is to be remembered also, that such vasomotor depression or exhaustion may persist for some time after the actual foci of infection have been removed. It is a clinically established fact that persistent post-infectious hypotension is extremely common.

Anemia.—The hypotension after hemorrhage is due to direct reduction in blood volume. In severe anemias, not due to hemorrhage, the blood-pressure is also apt to be low, in proportion to the cachexia and general weakness. There is probably an increase in the minute volume flow of the heart. Lerman and Means have recently studied the blood-pressure in 500 cases of pernicious anemia. There were only slight variations in averages due to age or sex, but compared to average figures for normal persons, the pressure was significantly lower. Indeed, they believe that hypotension is more frequent in pernicious anemia than in tuberculosis. It is associated with an almost complete disappearance of antecedent hypertension. The pulse pressures in pernicious anemia are higher than the corresponding ones in normal persons by from 9 to 17 millimeters Hg. This increased volume flow is compensatory, and gradually leads to cardiac hypertrophy. With improvement in the blood-picture, the pulse pressure tends to diminish.

Cachexia.—In advanced cachexias, hypotension is the rule. Deterioration in quantity and quality of the blood, anemia from repeated hemorrhages and myocardial degeneration would explain the low pressure. Ewing also refers to the fact that in certain carcinomata, particularly of the stomach, the anemia begins to dominate the picture, even taking on a secondary pernicious form.

HYPOTENSION IN CERTAIN CONSTITUTIONAL DIATHESES

Status Lymphaticus.—The hypotension in status lymphaticus is to be explained partly on the basis of the cardiovascular hypoplasia, with its resultant diminution in driving power. It may also stand in relation to the hypoplasia of the chromaffin system, which is, in all probability, part of this diathesis.

Infantilism.—The Lorain type of infantilism is now considered to be due to toxemia, the result of disease in intra-uterine life, or in early infancy. Its hypotension would thus be easily explained. In the Brissaud type there is lesion or dysfunction of one or more of the ductless glands. The hypophysis and thyroid are most commonly at fault, and the hypotension depends upon these dystrophies.

Myasthenia Gravis.—While it cannot be stated positively at this time that myasthenia is always dependent upon a thymus lesion, it seems established that there is a connection in a large proportion of the cases. Irradiation of the enlarged, or persistent thymus, with resulting involution of the gland, has been followed by marked improvement in the myasthenic symptoms, including the hypotension. In certain cases of myasthenia of the amyotrophic type, evidences of adrenal insufficiency have been found.

Adiposis Dolorosa.—There is still no agreement as to the cause of this condition. Atrophy of the thyroid, pluriglandular dystrophies involving thyroid, hypophysis, and adrenals, and lesions of the gonads, have all been found at autopsy. It has been emphasized that many cases of endocrine adiposity begin as a uniglandular disorder. The hypotension stands in relation to the ductless gland lesion.

HYPOTENSION DUE TO CERTAIN MECHANICAL FACTORS

Postural Change.—The change in position of the body from the recumbent to the erect posture throws a definite strain on the organs of circulation, determined by gravitation of the blood. Normally, on change from the recumbent to the standing position, the splanchnic vasomotor tone overcompensates the hydrostatic effects of gravity. Excessive fall of systolic pressure on change of position shows weakness of vasomotor control. Excessive rise of diastolic pressure denotes vascular spasm and abnormal effort. In postural hypotension, where there is excessive gravitation of blood to the extremities and the splanchnic area on standing, there is usually marked physical weakness and nervous instability. A most careful study of three such cases has been made by Bradbury and Eggleston. They believe that paralysis of the sympathetic vasoconstrictor endings is the underlying basis. Treatment was not of avail. More recently, Ghrist and Brown report two cases, one of which was greatly helped by ephedrin, 25 milligrams by mouth, hourly, for nine doses. These authors also advance the view that

postural hypotension represents a hypotonic state of the myoneural struc-
tures of the sympathetic and parasympathetic nervous system, of unknown
origin.

Body Habitus.—The assumption that asthenia and hypotension are
due to certain types of body habitus has been current for a long time.
Medical literature has teemed with articles on dropped stomach, ptotic
viscera, etc. Congenital and acquired forms have been described. Recently
careful studies have been made which must convince an impartial reader
that the drawing of sweeping conclusions as to fixed relations between body
build and body function are, to say the least, hazardous. Even though the
combination of asthenia, sagging of the viscera and weak circulation is
rather frequently found, it is not proved that the body habitus itself is
the cause of the symptoms, including the hypotension. The factors of myo-
cardial weakness and loss of vasomotor tone must be taken into account.
The malfunction of these factors often bears no relation to the body habitus
itself.

Effects of Exposure to High Temperature upon Circulation.—Low
blood-pressure in cases of heat exhaustion and some of the milder cases
of insolation is accompanied by the general picture of shock. Recent experi-
mental study on the effects of high temperature on man has shown that
there ensues marked dilatation of the peripheral vessels. This lack of resist-
ance in the periphery prevents the blood from returning to the heart.
The general picture of circulatory failure, and finally of shock, supervenes.
The chief factor in the hypotension is the relative diminution of blood
volume.

Variations in Atmospheric Pressure.—The remarkable adaptability
of the normal human mechanism to changed and changing conditions of
barometric pressure has been noted by various observers. Blood-pressure
studies at high altitude have shown that there is a primary fall of arterial
pressure. The drops are more marked in hypotensive than in normal indi-
viduals. Recent studies on blood-pressure during aviation have shown
that, where drops on pressure occur at high altitudes, return to normal
pressure occurs, and the phenomena of flight sickness disappear as soon
as oxygen is inhaled.

THE DEPRESSOR ACTION OF CERTAIN TISSUE EXTRACTS

It has been known for many years that various tissue extracts have a
depressor effect on blood-pressure. Oliver and Schaefer first demonstrated
such effects in 1895. Popielski, in 1909, described a substance which he
called "vasodilatin"; it could be isolated from stomach, small and large
intestine, brain, pancreas and thymus, and had a marked depressor effect.
In 1919 Abel and Kubota brought forward evidence to show that histamin
is a widely distributed constituent of animal tissues, organ extracts and

enzymatic products. It is, however, almost certain that histamin is *not* the only constituent of tissue extracts capable of lowering blood-pressure. For instance, it is not the active principle in the depressor liver extract. There is, however, no doubt that various tissues do contain substances which have a blood-pressure lowering effect. Much attention has been paid recently to liver extract.

Liver Extract.—The depressor substance in liver extract is probably non-protein in character. It is not histamin and not cholin, as shown by careful chemical tests. On experimental animals it has been found that marked drop in blood-pressure follows injection of the extract. Overdose kills the animal in one or two minutes, without convulsions. At autopsy the heart and lungs appear normal. The blood seems to have collected in the larger vessels. The effects of injection of liver extract in human beings with hypertension are now being studied in several clinics. Further study is needed to determine whether the extract will be valuable in the management of so-called malignant hypertension, or whether its effectiveness is limited to those more benign cases which frequently respond to regulation of the general regimen, with the addition of proper drug and dietary treatment.

ACTION OF CERTAIN GLANDULAR EXTRACTS

Parathyroid Extract.—Later reports on the parathyroid hormone indicate that the intravenous injection causes a slight fall in blood-pressure. The drop does not last long. There is apparently some diminution of blood volume. Subcutaneous injection of the extract does not cause a fall in pressure.

Insulin and Blood-Pressure.—In hypoglycemic conditions, vasomotor phenomena are common. Pallor or flushing, a sense of chilliness or of heat, and profuse sweating are present. At lower levels of blood-sugar, acute mental distress, delirium and coma supervene. In explanation of such manifestations, it appears that the stimulus set up by the decrease of the circulatory blood-sugar may act in certain nerve centers, notably in the region of the pons and medulla. There is also the possibility that the hypotension which follows the administration of large doses of insulin may act upon the cardiac factor in the maintenance of normal blood-pressure. The reduction in the amount of carbohydrate available for utilization by the heart muscle may so reduce its power that the asthenic picture supervenes.

Epinephrin and Blood-Pressure.—The intravenous injection of epinephrin causes a rise of blood-pressure. This is due, chiefly, to constriction of the vessels of the abdominal cavity. In addition there is some direct action on the heart. Small doses accelerate the heart rate and strengthen the output. In larger doses the acceleration may be excessive and may

impair the heart efficiency. Clinically, one indication for the use of epinephrin is in cases of marked hypotension due to vasomotor weakness, without cardiac depression. Its action is most prompt when given intravenously. It is, of course, also of great value where local constriction of vessels is desired.

Pituitary Extract.—Intravenous injection of pituitrin causes a rather slow rise of blood-pressure, which is maintained longer than the rise following injection of epinephrin. It is of value in cases in which the hypotension is due to loss of splanchnic vascular tone.

Gonad Extracts.—The ovarian field can point to no such persistent and systematic work of hormone isolation as we have in the cases of thyroid or pancreas. From the point of view of blood-pressure studies, it would appear that the ovary, during its period of functional activity, has a function in maintaining normal blood-pressure in women. Postmenopause hypertension, and its successful treatment by substitution organotherapy, are matters of clinical knowledge. The extract mechanism is not clear. In men it has been found that extirpation of the testes is followed by a fall of blood-pressure.

EFFECTS OF CERTAIN DRUGS ON BLOOD-PRESSURE

The Nitrite Group.—Different members of the nitrite group have an action on the circulation which is essentially similar. The variations in effect are those of promptness, intensity and duration of action—as illustrated, for instance, by amyl nitrite, sodium nitrite, and nitroglycerin. These drugs lower blood-pressure by their action on the arteries, which they cause to dilate by depressing the muscle of the arterial wall. The heart itself is not responsible for the change. The employment of the nitrites in hypertension is to be classed as purely symptomatic medication. They are essentially emergency drugs. They are of value in angina pectoris, where, at times, they may be combined with digitalis beneficially. They are also valuable in cases of threatened apoplexy or cardiac failure from hypertension. After intracerebral rupture has occurred, they are contra-indicated; the same rule applies also in marked hypotension from any cause.

Watermelon Seed.—Attention has recently been called to the depressor action of cucurbita citrullus (Barksdale). The toxicity of the drug is very low. Its action is rather slow but prolonged. The hypotension induced is due to capillary dilatation.

Quinidin Sulphate.—Large doses of quinidin sulphate probably depress the vascular sympathetic nerve endings. There is also definite dilatation of the peripheral vessels and capillary dilatation. It is, however, not probable that the pressure drop after therapeutic doses of quinidin is very marked.

Ephedrin.—Ephedrin is the active principle of an Asiatic drug, *Ma Huang*. It has physiological effects similar to those of epinephrin and tyramin. Its action is more prolonged, however. It can be given by mouth or subcutaneously. After its administration, systolic and diastolic pressure are raised and the heart rate slowed. It acts through peripheral stimulation of the sympathetic nervous system. Miller calls attention to its value in the treatment of bronchial asthma (relaxation of bronchial muscle spasm), and in certain cases of acute hypotension. Wilson studied its effect on the minute cardiac output of normal dogs, and found an immediate increase after its administration. Further study is needed to determine the full effects of the drug.

Strychnin.—Ordinary therapeutic doses of strychnin stimulate the vasomotor center directly. It is on this basis that there is justification for the use of the drug in conditions of low blood-pressure associated with marked depression of the vasomotor center. It is probably of no value in the hypotension of shock. Its therapeutic value would appear to be limited to such forms of circulatory weakness as are due to inefficiency of the vasomotor center.

ESSENTIAL HYPOTENSION

This is the name given to a syndrome, the chief objective finding of which is marked hypotension. Subjectively there are headache, vertigo and palpitation after even moderate exertion. There is marked fatigability, mental and physical. The cases cannot be classed under the psychoses; they do not present the picture of neurasthenia or psychasthenia. The condition occurs most commonly in early adult life, much more often in women than in men.

Various theories have been advanced to explain the hypotension. Hoxie believes that all of these patients have some obscure focal infection. Barach believes that the hypotension is due to respiratory deficit and decreased oxidation. Fossier ascribes it to body habitus. Mosenthal suggests that the hypotension may be due to the storage of excessive quantities of blood in the splanchnic vessels. Greaves also calls attention to the importance of the splanchnic pool in this type of hypotension.

Friedlander has submitted a theory, which may be summarized as a theory of capillary stasis, which has both clinical and experimental evidence to support it. This theory assumes that small quantities of histamin or histaminlike bodies are given off, perhaps in the intestinal tract, which act as capillary poisons. It is assumed that such poisons act as they do in the production of the hypotension of shock. This general view of capillary stasis and its possibilities has been distinctly strengthened by the researches of Krogh on capillary circulation.

Considerable evidence has been accumulated to justify such a view of the low blood-pressure in essential hypotension, though much work

must be done before this hypothesis may be said to rest upon the basis
of established fact.

HYPOTENSION DUE TO MALFUNCTION OF FACTORS NORMALLY MAINTAINING BLOOD-PRESSURE

The Cardiac Factor.—Temporary hypotension due to the failure of
the cardiac factor is easy to understand as, for instance, in typhoid fever.
In chronic heart disease, however, failing circulation may be associated
with a normal or even an increased blood-pressure, owing to compensatory
constriction of the peripheral arterioles. This peripheral vasoconstriction,
however, necessarily reduces the capillary blood-flow. The inability to
increase the capillary flow during exercise is responsible for the muscular
weakness and asthenia found with decompensated hearts. Also, the hyper-
trophied heart is from the beginning a diseased heart, without proportionate
increase in its own blood supply. Its reserve power is reduced rapidly,
especially when myocardial degeneration supervenes. Hypotension usually
ensues in the later stages of myocardial degeneration. What does happen
early is that the diastolic pressure rises, causing marked diminution in
pulse pressure. As Eyster has pointed out, ventricular incompetence super-
venes when the initial load on the ventricle, represented by the venous
pressure, exceeds the physiological limit of the muscle to respond to an
increased load by increased work. The smaller the pulse pressure, in
myocardial disease, the lower the limit of cardiac reserve. Sudden drops
in blood-pressure in hypertensives are usually of serious prognostic
omen, because they indicate rapid weakening of cardiac power.

Hypotension is common in some of the cardiac arhythmias. In attacks
of essential paroxysmal tachycardia, the hypotension is due to insufficient
filling of the ventricles, with reduced minute volume flow.

In bradycardia, especially in heart-block associated with Stokes-Adams'
syndrome, the pseudo-hypotension is due to the continued outflow of blood
during the long diastole.

In premature contractions, the association of hypotension, *ceteris
paribus,* is evidence of functional nature of the arhythmia.

In auricular fibrillation, absolutely accurate estimations of systolic
and diastolic pressures cannot be made. The average pressure may, how-
ever, be estimated. The pressures in the arteriosclerotic group are higher
than those in the rheumatic group. Average systolic pressures of over
160 millimeters in the sclerotic groups, and of over 110 millimeters in the
rheumatic group, are of good omen. A falling average pressure makes the
outlook graver.

The Condition of the Vessel Walls.—Flaccid and toneless muscle
fibers in blood-vessel walls, due to the influence of acute infection, may
be a factor in acute hypotension. German writers refer rather frequently

to so-called "hypotonia." The hypotension accompanying this condition is said to be due, in large measure, to weakness of the arterial wall. It must also be remembered that low blood-pressure is not uncommon in certain cases of arteriosclerosis. Here the blood flows through the vessels as does fluid through unyielding tubes. In such cases there is no periodic distention or contraction of the lumen, and tension is therefore lowered.

Peripheral Resistance Determined by Vasomotor Tone.—It is believed by many observers that the peripheral resistance to the blood stream is the most important single factor in the regulation of blood-pressure. The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or depressor action on vasomotor function. The capillaries play a very important part in the production and maintenance of vasomotor tone. Thus, syncope may be due to loss of tone in capillaries and veins. Sudden changes in the tone of the abdominal vessels are particularly apt to produce sudden hypotension. Capillaries possess powers of dilatation and constriction independently of the arterioles. Normally, they maintain a state of constrictor tone. The factors entering into the mechanism of varying capillary constriction and dilatation are nervous and chemical stimulation. Nervous stimuli cause only constriction. Chemical stimuli may mediate both constriction and dilatation. The amount of blood which may, under circumstances, be stored in the capillary bed, instead of being returned to the general circulation, is very large. There is suggestive evidence that the capillaries are normally kept tonically contracted through the agency of the pituitary hormone. The fundamental importance of the capillaries in the production of shock, and its accompanying hypotension, has already been discussed. A possible explanation of the low blood-pressure in essential hypotension, based on capillary poisoning by histamin, has been mentioned. Capillary stasis is of prime importance in heart failure. The blood-flow in the capillaries is a measure of the efficiency of the circulation. The constitutional shock symptoms of burns, occurring before the period of infection, are due to material absorbed from the surface. An enormous capillary bed, potentially closed under normal conditions, is opened up by a first or second degree burn. From the standpoint of therapy this is of importance. A new field in medicine is opening up through the study of the activities, physiological and pathological, of the capillaries.

HYPOTENSION IN RELATION TO ENDOCRINE DISORDERS

Adrenal Insufficiency.—Physiologists maintain that the adrenal medulla is not essential to life, while the preservation of only a very small portion of the cortex may be compatible with apparent health and vigor. With reference to the hypotension of adrenal insufficiency, the physiologists point out that epinephrin is given off from the medulla and not from

the cortex, that the maintenance of normal pressure does not depend to any important degree upon epinephrin. Hypotension is not caused even when the epinephrin output is totally suppressed. Fatal adrenal insufficiency is produced in animals by interference with the cortex.

There is no agreement between physiologists and clinicians as to adrenal insufficiency and the mechanism of its production. Clinically, three types of adrenal insufficiency are described: (a) The fulminating rapidly fatal form, (b) the myasthenic form, and (c) subacute and chronic forms, including Addison's disease. Tuberculosis may induce any one of these forms. Syphilis not infrequently attacks the adrenals. So also does the virus of certain of the acute infections. Attention has also been called to the fact that, at times, extreme adrenal insufficiency produces a clinical picture suggestive of acute poisoning. Chronic insufficiency is revealed by hypotension, skin bronzing and myasthenia. The muscle fatigability is marked, and in advancing cases is changed to muscle cramps, contractures and terminal convulsions.

It must be admitted that the mechanism of the production of these symptoms, including the hypotension, is not clear. And it should be added that the clinical claims of results achieved by substitution organotherapy do not seem to rest upon the basis of carefully controlled study and critical analysis.

The Pituitary Gland.—It has been known for some time that certain types of dyspituitarism, notably certain types of hypopituitarism, are associated with low blood-pressure. In the light of recent studies by Krogh and others, indicating that the pituitary hormone has to do with the maintenance of arterial pressure, largely through its action on the capillaries, this clinically established fact finds an explanation. The association of infantilism with hypotension has already been noted. In those forms of hypopituitarism which manifest themselves in early adult life, asthenia and hypotension are outstanding features. The relation of gonads to blood-pressure has already been discussed.

Pluriglandular Disturbances.—The present tendency to blame the endocrine glands for all forms of asthenia is distinctly unfortunate. The extravagant claims as to the value of substitution mixed gland treatment made by some clinicians are countered by sharp criticism on the part of physiologists and biochemists. It is pointed out that *proof* is not available to show that numerous glands are affected in such ways as to produce various clinical syndromes. Abel has rightly raised his voice against what he has termed "the stampede to the pluriglandular gold fields." Lisser refers to the "pluriglandular three-ringed circus" and adds that "in the enthusiasm for roping these glands together a veritable jumble of knots has been tied that is difficult to entangle."

The explanation of asthenia and hypotension due to pluriglandular dysfunction or disorder is not at hand. As Lisser sees the future of organo-

therapy, progress will depend upon carefully planned, united efforts of physiologists and clinicians. In such studies there must be neither ignorant credulity nor cynical intolerance.

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CHAPTER L

THE TREATMENT OF THROMBO-ANGIITIS OBLITERANS
Samuel Silbert

There is a prevailing impression that thrombo-angiitis obliterans is a progressive disease which practically always results in the loss of one or more extremities. The etiology has been looked upon as unknown and therefore a rational method of treatment has been impossible. If one were to judge by the outcome in the cases treated by earlier methods this hopeless outlook would be entirely justified, for over 85 per cent of these patients have lost one or more extremities. The duration of life in these cases from the time of the onset of symptoms has been from five to twenty years. But the experience gained from observing several hundred patients in recent years under changed methods of treatment has led me to the conclusion that the disease can be checked, that patients can be improved and entirely relieved of symptoms, and that amputations can be averted in the great majority of cases.

Accumulating evidence from my experience has led me to support the view that the most outstanding factor in the etiology of thrombo-angiitis obliterans is poisoning from the use of tobacco. Constitutional susceptibility to this poison is undoubtedly present, for the vast majority of smokers obviously escape the disease. It may be that this predisposing constitutional factor is a disturbance of the endocrine system. The only direct and specific method of combating the illness is to absolutely prohibit the use of tobacco in any form. Cessation of smoking tends to bring the progressive course of the disease to an end, and allows nature's spontaneous effort for restoration of circulation to exert itself. In some of the early cases this appears to be all the treatment that is necessary, for we often see patients in whom healing of ulceration has taken place and collateral circulation has developed without any other form of treatment.

Since spontaneous improvement occasionally occurs, it is essential to view with skepticism hasty conclusions as to the value of methods of treatment. Numerous cases classed as improved under different forms of therapy have relapsed in a few months and progressed rapidly to gangrene and amputation. For the purpose of establishing a standard for rationally judging the value of various treatments, I made a study of the spontaneous course of thrombo-angiitis obliterans in a series of 258 untreated cases. I found that 77 per cent of 155 patients with this disease required ampu-

tation of one extremity in a period of five years from the onset of symptoms (Table I). With this knowledge of the spontaneous course, comparison can be made with the results obtained under a single method of treatment. Therapeutic success must be judged by the ability to reduce the number of amputations required in a corresponding period. In a series of over 200 cases treated over a varying period of from one to five and one-half years by the method of the writer, less than 10 per cent have thus far required amputation. These 10 per cent are made up of cases whose condition was far advanced when first seen. It can be stated with complete confidence that if cases of thrombo-angiitis obliterans were recognized in early stages of the disease and proper methods of treatment instituted, amputation for this malady would become a rare event.

TABLE I—SPONTANEOUS COURSE OF UNTREATED THROMBO-ANGIITIS OBLITERANS

Cases without amputation followed over five years after onset.....	18
Cases amputated after five years from onset.....................	17
Cases amputated within five years from onset...:..............	120
Total of cases followed for sufficient period....,..................	155
Percentage of cases requiring amputation within five years......	77

The prognosis under treatment depends upon the extent of circulatory deficiency. It is usually not possible to determine the degree of impairment in circulation by palpation alone, and therefore a mechanical means of measuring the blood-flow is of great assistance. The Pachon oscillometer is a useful instrument for this purpose and with it the early cases can be readily distinguished from the advanced. In a recent study of this matter, a division of all cases under treatment was made into two major groups according to their oscillometric readings on first examination. The first group included patients who had, at the ankle of the affected extremity, a reading on the oscillometric scale of one-half or more; the second group consisted of all cases whose readings were zero or less than one-half at this level. The subsequent course of these patients demonstrated that all in the first group have an excellent prognosis, and that the outlook in the second group is progressively worse as the clinical condition is more advanced. When gangrene is already present and the oscillometer reading is zero, amputation can seldom be averted (Table II).

The outcome in thrombo-angiitis obliterans depends upon the rapidity of development of a collateral circulation sufficient to maintain the nutrition of the affected extremity. If formation of collateral circulation keeps pace with the obliterative process, gangrene does not occur, but if it falls behind, the nutrition of the tissues becomes inadequate and necrosis results. The aim of the writer's method of treatment is to assist and hasten nature's spontaneous effort to produce a collateral circulation, as it is upon the speed of this process that the outcome depends. The mechanical effect

TABLE II—RESULTS OF TREATMENT IN THROMBO-ANGIITIS OBLITERANS

Group	Number of Cases	Symptomatic Improvement	Oscillometric Improvement	Ulcers Healed	Amputations
Group 1 (osc. read. ½ or more)					
A. Pain only	20	20	9	..	0
B. Pain with ulceration	9	9	3	6	0
C. Pain, ulceration and gangrene	3	3	2	3	0
Group 2 (osc. read. less than ½)					
A. Pain only	63	51	14	..	1
B. Pain with ulceration	22	17	3	13	3
C. Pain, ulceration and gangrene	7	1	0	0	5
Totals	124	101	31	22	9

of an increased volume of blood produced by repeated injections of hypertonic salt solution is utilized for this purpose. The result of this increase in volume is a dilatation of existing vascular channels and opening up of new areas of capillary circulation. No specific effect is expected from the salt which is employed and therefore the least toxic substance is the one used.

The technical procedures of this method are simple. The saline used is 5 per cent sodium chlorid made up in freshly distilled water, filtered, and immediately sterilized. Since bacteria grow readily in distilled water, it is of the utmost importance that the solution be sterilized as soon as possible. A solution prepared in this manner, and kept in a cotton-stoppered flask, will not deteriorate and can safely be used for a week or more. The simplest method of sterilization is boiling in a water bath for fifteen minutes, with a second sterilization in about eight hours, thus eliminating the possibility of failure to destroy resistant spores. If the solution is to be kept for any length of time, daily resterilization is a wise precaution. I have used this method satisfactorily for over five years.

Injections are given by the gravity method, using an ordinary 300 c.c. salvarsan cylinder with connecting tube and eighteen-bore intravenous needle. Injections are given either in the superficial veins of the arm or of the neck, with the patient lying down. The first dose is 150 c.c., and all subsequent injections are 300 c.c. The injection should usually take from seven to ten minutes. Care must be exercised to avoid infiltration of the tissues with the salt solution, as this causes considerable pain. A single vein may be used again and again without the occurrence of thrombosis. If thrombosis does occur, it may be due to the fact that the solution has been allowed to become too concentrated, or that the patient has not stopped smoking. To relieve the apprehension of sensitive patients, the

infiltration of a drop of novocain at the site of the injection, before using the larger needle, is a good practice.

Injections are given three times a week at the start, then twice, and later once a week. They may be further reduced as improvement takes place. Patients may be allowed to get up immediately after the treatment and return to work, and they are encouraged to continue with their usual occupations. In this way one of the disadvantages of a prolonged course of treatment is minimized. The only changes noted by the patient during treatment are thirst and a general feeling of warmth. Flushing of the face and engorgement of the superficial veins take place. Excretion of the 15 grams of salt requires forty-eight hours, and therefore injections should not be given more often than three times a week. Febrile reactions following injection indicate the presence of foreign protein in the solution. This foreign protein is usually the result of the growth of bacteria in the distilled water before the solution is sterilized.

The administration of repeated injections of hypertonic salt solution produces a certain amount of blood destruction, but as the majority of patients with thrombo-angiitis obliterans have a high hemoglobin and red cell count, this is of no serious consequence. An anemia sufficient to give symptoms has never been produced even in patients treated for a long time. No injury to heart or kidneys has ever been seen in spite of prolonged treatment of many cases. Definite cardiac or renal impairment are contra-indications to the use of this method; if irregularity of pulse develops during an injection, the treatment should be stopped. I do not believe it is wise to undertake it in patients over sixty years of age. Over thirteen thousand injections have been given under my direction without a fatality or serious reaction.

Improvement may be noted very soon after beginning treatment, but usually not until after a few weeks. Occasionally treatment must be continued for several months before definite evidence of improvement is seen. The first subjective evidences of benefit are usually the increase in warmth of the extremities and diminution of pain. The first objective changes are increase in the temperature of the extremity and improvement in nail growth. Later, healing of ulceration and development of pulsation in previously occluded or collateral vessels are noted. Likewise, a gain in weight and improvement in the patient's general health regularly take place. Relief of pain and healing of ulcers occur with great regularity. Improvement in walking likewise takes place, but favorable progress in this respect is frequently slow. Perseverance is necessary if one is to obtain satisfactory results in the treatment of these patients. The most gratifying results are obtained with the early cases, as these show a rapid and striking improvement.

Additional measures to improve the circulation may be tried, and some of them are of value. These consist of rest in bed, hot foot baths, baking,

diathermy, and the exercises recommended by Buerger.[1] X-ray treatment over the lower spine has been suggested, but has failed to prove of value in the cases under my direct observation. The use of subcutaneous injections of insulin and large quantities of nitroglycerin by mouth are being tried, but no final statement as to their value can be made at present. The Leriche operation, sympathectomy, has proved a failure in every case in which I have seen it done. The operations of ramisection and adrenalectomy are too serious and are unnecessary as better results are obtained by non-operative measures.

To relieve pain is one of the major problems in treatment, and the success or failure to save an extremity frequently hinges on the ability to cope with this symptom. Fortunately the periods of severe pain occur only in a minority of patients and seldom last more than a few weeks. The pain may suddenly subside without any obvious change in the objective condition. Rest in bed and sedatives must be used during this stage. Aspirin, luminal, codein or morphin, either singly or in combination, may be tried. A suppository composed of codein, 1 grain, and veronal, 10 grains, is frequently valuable. Intravenous injections of typhoid vaccine sufficient to produce a sharp temperature reaction, may be helpful in this as in other painful conditions. The first dose should not be more than five million bacteria and each subsequent dose can be doubled. These injections may be given every other day. Subcutaneous injections of insulin, 10 to 15 units, two or three times a day, may also be of value in the relief of pain. Injections of insulin should always be preceded by a glass of orange juice or a bar of chocolate to guard against insulin shock.

The keynote of surgical treatment should be conservatism. Operative measures should be deferred as long as possible, so as to allow time for collateral circulation to develop. The majority of patients can be saved from amputation of their legs by allowing nature to perform a spontaneous

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[1] "The affected limb is elevated with the patient lying in bed, to from 60° or 90° above the horizontal, being allowed to rest upon a support for from thirty seconds to three minutes, the period of time being the *minimum* amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about three to five minutes, during which time an electric heating pad or a hot water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes. These cycles are repeated over a period of about one hour, some six to seven cycles constituting a seance.

"The number of seances cannot be categorically stated but should vary with the case. In a general way they should occupy at least six to seven hours a day, that is every alternate hour during the daytime. During the hours of rest, heat is applied continuously in the form of an electric pad, hot water bag, hot air apparatus, or electric lamp." Leo Buerger, *Circulatory Disturbances of the Extremities*, Philadelphia, W. R. Saunders Company, 1924.

amputation of a gangrenous toe. A major amputation should be resorted to only in the face of rapidly spreading gangrene. Even in the presence of infection and ascending lymphangitis, simple drainage and treatment with wet dressings should be tried and gratifying results are very frequently obtained. Local ulcerations should be kept clean and dressed with simple vaseline dressings. Antiseptics and local anesthetic ointments are dangerous as the tissues are devitalized by undernourishment, and gangrene may result from their use. For the same reason, trauma and infection must be guarded against, for the impaired circulation is insufficient to meet the extra demands of such accidents.

Unfortunately patients are constantly presenting themselves with the disease so advanced that it is impossible to save the extremity. Such cases should be treated intensively with intravenous injections for two or three months if possible. Amputation below the knee may then be found to be successful. In nine successive cases treated in this manner, I have had no failures in low amputations and all of these patients except the last one (recently amputated) are now satisfactorily wearing artificial legs.

It is of the utmost importance to perform an amputation below the knee as a patient is decidedly less crippled by such an amputation than by one at or above the knee. A patient with an amputation below the knee can wear an artificial leg and walk without the use of a cane, and is not conspicuously crippled. The entire economic future of the patient may depend upon this point as the obviously crippled individual has difficulty in obtaining employment. Five inches or more of stump should be left in order to make possible the satisfactory fitting of an artificial leg.

In performing low amputations it is important to make a combined skin and muscle flap and to avoid unnecessary traumatization of the tissues. Attempts at plastic operations on the bone are unnecessary and unwise as they imperil the healing of the stump. The wound should be sutured with minimal drainage as stumps which are left open may require months to heal. When the above precautions are observed, rapid and satisfactory healing will usually take place.

RECENT ADVANCES IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

SAMUEL C. HARVEY AND ASHLEY W. OUGHTERSON

The treatment of peripheral vascular disease has recently received considerable stimulus from the work of Leriche followed in turn by that of Royal and Hunter, and Adson and Brown. As a better understanding of the physiology of the arterioles and capillaries has been developed, it has become evident that a better functional classification is needed so that more rational therapy may be selected for specific groups. The classification adopted by Brown best fulfills this need.

TABLE I—TENTATIVE CLINICAL CLASSIFICATION OF ARTERIAL VASCULAR DISEASES *

Functional or vaso-motor types	Local distribution	Vasoconstricting types	1. Multiple-phase color reaction; Raynaud's disease 2. One-phase color reaction; acrocyanosis, dead finger, local syncope
		Vasodilating types	Erythromelalgia
	General distribution	Vasoconstricting types	Primary or essential hypertension (early stages)
		Vasodilating types	Primary or essential hypotension
Organic types	Local distribution		1. Arteriosclerosis, endarteritis obliterans, with or without thrombosis; diabetic gangrene 2. Thrombo-angiitis obliterans 3. Simple thrombosis or embolism 4. Arteritis of known infectious origin (rheumatic † syphilitic) 5. Aneurysm with or without thrombosis
	General distribution		Arteriosclerosis 1. Primary 2. Secondary to hypertension

* Allen and Brown, *Am. J. M. Sc.*, 1927, 175:319-329. See References.
† A pathologic rather than a clinical entity.

It is not necessary here to repeat the detailed symptomatology which has been given in Volume V, but rather to emphasize certain pitfalls in

the differential diagnosis. The majority (90 per cent) of patients with peripheral vascular disease can be classified as either of the organic or vasomotor type according to the absence or presence of pulsation in the larger arteries. In the remainder the diagnosis must be made on the general picture. Some of the more important factors to be considered are the age and sex of the patient, and whether the gangrene is of sudden onset as in an obliterative lesion. Do the symptoms disappear or improve with local and environmental heat, and what are the accompanying vasomotor changes, if any? In Allen and Meyerding's series 80 per cent of the cases had been incorrectly diagnosed. This factor alone would account for the great variation in opinion as to the efficiency of any given form of treatment. It should be remembered that vasomotor disturbance may be an early sign of obliterative vascular disease. There are a considerable number of cases of thrombo-angiitis obliterans in whom pulsation may be present in the main arteries of the feet. The diagnosis of Raynaud's disease should be based on evidence of a defect of the vasomotor mechanism without vascular occlusion rather than on conformity to a general clinical picture. Arteriosclerosis may be superimposed on other vascular disturbances in patients over forty-five, and its incidence increases with the age.

The etiology of most types of vascular disease still remains unknown, hence we have no specific therapy except for those long recognized as due to luetic infection. The advances in the treatment of these diseases have been based on a clearer conception of the pathology and physiology of the peripheral vessels. Hence it becomes necessary, in order to treat a given lesion successfully, to have a clear understanding of the primary pathology and the stage to which it has progressed. It is likewise necessary to differentiate the functional from the organic type and if there is a mixture of these to have an appreciation of the relative degree of functional or organic involvement. The expectancy of relief from a given treatment as well as the prognosis hinge upon these factors. The importance of a careful history and painstaking physical examination of the extremities is therefore manifest. Certain procedures and instruments of precision have been added to the armamentarium of the physician in order to obtain more precise information of the condition of the peripheral vascular system. Among these may be mentioned the sodium iodid injection of Brooks. While undoubtedly the information obtained in certain cases is of value, the safety of the procedure is very questionable as has been pointed out by Singleton. The oscillometer, as described by Samuels and Silbert, furnishes an accurate means of recording the pulsation of the vessels and is of assistance in following the progress of the disease and aiding in the prognosis. The Stewart calorimeter, as used by Brown, has contributed much valuable information on the rate of heat elimination of the extremities.

A great number of therapeutic procedures have been described, and

TABLE II—DIFFERENTIAL DIAGNOSIS OF VASCULAR DISEASE AFFECTING THE EXTREMITIES [*]

	Thrombo-Angiitis Obliterans	Arteriosclerotic Disease	Raynaud's Disease and Similar Conditions	Primary Erythromelalgia
Pulsation of peripheral arteries	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Normal	Normal
Excessive rubor with dependence	Present	Present	Absent	Absent
Excessive pallor with elevation	Present	Present	Absent	Absent
Claudication	Usually present	Usually present	Absent	Absent
Gangrene	Common	Common	Absent	Absent
Rest-pain	Usually very severe	Usually mild	Rare	Never
Type of rest-pain	Sharp, stinging	Aching	Usually absent	Usually mild
Appearance of gangrenous ulcers	Moist, inflamed, discharging	Dry	Absent	Burning
Superficial phlebitis	30 per cent of cases	Absent	Small punched-out areas	None
Age at onset of symptoms	Mostly between twenty-five and forty-five years	Mostly between fifty-five and eighty-five years	Absent	Absent
Sex	Males 99 per cent	Males 90 per cent	Mostly between seventeen and thirty-five years	Mostly between thirty and fifty years
Race	Hebrews 50 per cent	Any	Females 95 per cent	Females 70 per cent
Roentgenographic appearance of arteries	Usually no sclerosis	Usually sclerosis	Any	Any
Color changes following exposure to cold	30 per cent	15 to 20 per cent	Normal	Normal
Temperature of extremities	Low	Low	Always	Never
Edema	Frequent	Infrequent	Low	High
			Absent	Absent

* Allen and Brown, Ann. Int. Med., 1928, 1 : 535-549, 550-556.

frequently overenthusiastic claims have been made by their authors. The criteria by which a successful therapeutic procedure should be judged, has been well pointed out by Silbert who studied the spontaneous course of a large group of patients with thrombo-angiitis obliterans. He found that 77 per cent of this group came to amputation within five years from the onset of symptoms, and states that "satisfactory claims for therapeutic success must rest on comparison of results obtained in a group of patients followed for a period of five years with those of the spontaneous course of the disease." The basis for the claim of successful treatment for each procedure should be kept in mind, whether it is the preservation of life, the improvement of the circulation, or the relief of pain. Gangrene and the resulting amputation may be delayed or, following a given treatment, it may be possible to amputate at a lower level or to obtain primary and permanent healing of the stump.

TREATMENT

The following is a brief résumé and a tentative classification of the methods of treatment in vogue at the present time.

1. **General Health of the Patient.**—As has been pointed out by Meleney and Miller, the ultimate outcome depends upon the race between the collateral circulation and the progress of the disease. While the underlying pathology of thrombo-angiitis obliterans is unknown, the evidence available indicates that it is probably of infectious origin or at least that infection plays a prominent rôle in the obliteration of the vessel and hence any factor which tends to raise the general resistance of the individual may be beneficial.

2. **Etiology.**—In spite of numerous and varied theories, the etiology of thrombo-angiitis obliterans and Raynaud's disease is still unknown. While the possibility of smoking as a causative factor is open to argument, the experience of a large number of clinicians, who state their convictions that whatever the underlying cause prolonged smoking is the immediate causative factor in the production of the disease, cannot be overlooked. Silbert (1928) states: "Repeatedly, failure to improve under treatment has been noted in men who continue to smoke, and prompt improvement began when they were finally induced to stop." Raynaud's disease is frequently associated with a neuropathic constitution and attacks are likely to be brought on by an emotional upset.

3. **Attempts to Alter the Physical Character of the Blood.**—This general term is used for such procedures as the intravenous injection of sodium citrate and sodium chlorid as well as the older forms of treatment by introducing fluids subcutaneously or by duodenal tube. The treatment, particularly the intravenous use of sodium chlorid, is undoubtedly effica-

cious, but the underlying physiology is not understood. Silbert, in 1926, reported a series of cases of thrombo-angiitis obliterans which were followed for a five-year period with a marked reduction in the number which came to amputation. These were treated with hypertonic saline administered intravenously. Considering the relatively small amount of saline administered to the blood volume it is difficult to believe that the good results reported are due to an alteration of the viscosity of the blood, but rather to some other, as yet unknown, mechanism.

4. **Attempts to Alter the Vasomotor Mechanism.**—Various procedures have been developed to abolish the vasoconstrictor spasm of the peripheral blood-vessels as severing their control by the sympathetic nervous system. This treatment is efficacious only when the functional component is predominatnig and in Raynaud's disease finds its greatest usefulness. However, in about 10 per cent of the cases of thrombo-angiitis obliterans, vasoconstrictor disturbances with color changes similar to Raynaud's disease are superimposed on the organic lesion. In this group one may therefore expect beneficial results if the vasoconstrictor spasm is abolished.

Among the procedures used to accomplish this is periarterial sympathectomy as advocated by Leriche. This operation undoubtedly produces vasodilatation lasting for a variable period but never more than a few months. It is probably most efficacious when used for the relief of the pain which so frequently is the predominating symptom in peripheral vascular disease and particularly in thrombo-angiitis obliterans. It also apparently exerts some trophic influence on tissues and has been used with a high incidence of cure in treating refractory ulceration, but again the results are temporary. Muller has reported his end results which are characteristic of most of the other reports of peripheral sympathectomy and are summarized in Table III:

TABLE III—PERIARTERIAL SYMPATHECTOMY
(December, 1919–March, 1928: 90 operations, 72 patients)

Disease	Cases	Relieved
Thrombo-angiitis obliterans	17	2
Arteriosclerotic gangrene (senile and diabetic)....	12 [1]	2
Raynaud's disease	3	2
Scleroderma	3	0
Trophic ulcer	10	6
Leg ulcer	7	5
Painful stump	4	2
Miscellaneous	16	6
TOTAL NUMBER	72	25
Per cent		34.7

[1] One death (1.4 per cent).

The procedure has been largely discarded for those which yield more permanent results.

Ramisection as used by Hunter and Royle in the treatment of spastic paralysis has been tried less extensively but with apparently somewhat better results than the Leriche operation. Fulton has recently reported a favorable case, carefully studied, in which this method was used. However, the complete removal of the ganglia of the sympathetic system supplying an extremity, as practiced by Adson, has given the most satisfactory results and in a few instances of Raynaud's disease has resulted in a complete relief of pain and a permanent elevation of the temperature of the extremity. Adson and Brown have reported excellent results with this operation in certain selected cases of thrombo-angiitis obliterans. The intravenous injection of foreign protein (typhoid vaccine), if given in doses sufficient to produce a hyperthermia of 1 to 2 degrees, likewise causes a similar vasodilatation and increased temperature of the extremity, which in some instances may last several months. Brown, Allen and Mahorner have used this as a test in selecting cases of thrombo-angiitis obliterans with a functional element suitable for ganglionectomy. Allen and Smithwick believe that "it hastens the development of a collateral circulation more effectively than any conservative measure heretofore suggested." Phillips and Tunick have reported excellent results of a similar character with Roentgen ray therapy applied over the region of the sympathetic ganglia supplying an extremity, but in other hands this treatment has not been so encouraging.

5. **Attempts to Improve Collateral Circulation.**—While this is accomplished indirectly by the above treatment, the term is here used for those procedures that are directly aimed at increasing the collateral circulation. The exercises described by Buerger in his book, are unquestionably effective to a certain degree. More radical procedures are the ligation of the femoral artery just distal to the profunda as practiced by Lewis and Reichert, and ligation of the popliteal vein as described by Morton. There is still some doubt as to whether these operations are worth while.

6. **Amputation.**—While this is the oldest effective form of treatment which can always be resorted to as a last measure, it is mutilating and may spell economic disaster. The criterion of success of the above procedures is whether amputation can be avoided, delayed, or obtained successfully at a lower level, or whether pain can be relieved. It should be emphasized that in the past amputation has not always been used as a last resort measure nor has it been adequately supplemented by such procedures as those outlined above. For example amputation below the knee to obtain a functional joint is desirable if the limited extent of the lesion will permit it. The criteria as to the possibility of a successful amputation below the knee, such as pulsation of the popliteal, are not infallible. The lesion must be limited to the foot, and even then, as reported by Allen and Meyer-

ding, the best that can be promised is an 80 per cent chance of healing. This figure may be materially influenced by both pre- and postoperative use of the above methods of treatment. On the other hand, there are instances, as in the presence of infection with gangrene due to arteriosclerosis and diabetes, where delay may be fatal. If there is evidence of a possible arteriosclerosis superimposed on a vascular lesion of another type, it is better to go above the knee. Incision or removal of a toe nail is a dangerous procedure. In a series of one hundred cases (Allen and Meyerding) gangrene was initiated in 35 per cent by this simple minor procedure. Amputation of the toes may be indicated where there has been a sudden thrombosis of the vessels of the toe, leaving a pulsating pedal artery and a normal skin at the line of amputation. The foot should never be amputated as healing at this level is very poor. It should be remembered that the course of Raynaud's disease and thrombo-angiitis obliterans is not infrequently self-limited and that if the disease is not arrested, a considerable number of the cases, by development of the collateral circulation, reach a stage of adequate compensation.

7. **Treatment of Local Lesions.**—Mycotic dermatitis of the extremities, as described by White, is not infrequently associated with peripheral occlusive endarteritis and at times may be one of the first symptoms of vascular disease. Local preparations are useful, but too strong preparations must be avoided. Wet dressings and local Roentgen ray treatment are dangerous. The dermatitis usually diminishes as the circulation of the extremity improves. As pointed out by Meleney and Miller, baking, a form of therapy frequently indulged in, may result in the lighting up of a focal infection. However, this risk can be considerably lessened by painstaking care of the skin and nails, keeping them clean and soft. The care of the skin and nails is one of the most important steps in prophylaxis against infection and gangrene, and too frequently overlooked.

The prognosis of peripheral vascular disease has in recent years steadily improved in contrast to its former hopeless outlook. This is particularly true of thrombo-angiitis obliterans and Raynaud's disease. Early diagnosis and early treatment are the *sine qua non* for a successful outcome. Medical treatment is expensive and long drawn out and where the economic factor is paramount, conservative amputation in unfavorable cases may still be in the best interest of the patient. However, the incidence of amputation in these diseases is being slowly but steadily reduced.

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CHAPTER LII

DISEASES OF THE ESOPHAGUS

Chevalier Jackson and Chevalier L. Jackson

Introduction.—The development of the technic of esophagoscopy has revolutionized the diagnosis and treatment of esophageal diseases. It has been the development of the technic rather than the instrument itself that has brought about the revolution. When the esophagoscope first appeared it was not realized that, if inserted into the pharynx and pushed upon, the one place it would never go was into the esophagus. Disaster resulted. Consequently the study of the diseases of the esophagus by direct inspection awaited the development of a technic that would render it safe. This development has reached such a degree of perfection that the esophagus of any human being, at any age, can be safely inspected in a few minutes without any anesthetic, general or local. The safety of esophagoscopy by the modern technic is shown by the statistics of the Bronchoscopic Clinics of Philadelphia. Of the last 6275 esophagoscopies done by five individual endoscopists there has been no death due to the insertion of the esophagoscope considered apart from the condition for which esophagoscopy was done.

Symptoms of Esophageal Disease.—Dysphagia, odynphagia, regurgitation, hematemesis and pain are the clear and definite symptoms. Secondary symptoms are weight loss, emaciation, cachexia, and dehydration. Even more important than any of these, because earlier, are vague indefinite sensations that the patient cannot clearly describe.

It is necessary to distinguish between *odynphagia,* painful swallowing, and *dysphagia,* difficulty in swallowing. The difficulty may be with liquids or solids, the odynphagia may be noted with either liquids or solids or it may be only with cold or with hot foods or drinks. The patient may deny difficulty in swallowing when close questioning will reveal the fact that the food does not "go all the way through to the stomach." *Regurgitation* is usually called *vomiting* by the patient who does not realize the distinction between food that has and food that has not reached the stomach. The regurgitant act may mix stomach contents with foods retained esophageally. The regurgitated materials may be only a few small particles or as much as a quart or two. *Hematemesis* may be only a streak of blood in food or secretions, spat out; it may be a pint or more of bright crimson fluid or clotted blood, or it may be of brown "coffee

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grounds" appearance. *Esophageal* pain is not always felt in the esophagus. The characteristic pain is an aching referred vaguely to the region behind the sternum and extending through to the back. *Weight loss, malnutrition, emaciation* and *dehydration* are late symptoms and are due not only to the obstruction but to the malnutrition resulting from ill-balanced diet, lack of fruit juices and vegetable soups, the need for which is often overlooked. It has been discovered at the Philadelphia Bronchoscopic Clinics that malnutrition will follow failure to get saliva into the stomach (Jackson, *Arch. Pediat.*). *Dehydration* is a very dangerous condition often overlooked as a symptom. It is manifested by a dry, wrinkled parched skin and mucosa, and scanty urine; later, stupor and coma appear. *Vague esophageal symptoms* are described by the patient as a "lump in the throat," "something rising in the throat," "my swallow does not seem to be quite right." These symptoms may be overlooked by the patient; if mentioned, they are usually attributed erroneously to hysteria.

Diagnosis of Esophageal Diseases.—There are only two diagnostic means of value; they are: (1) the Roentgen ray, and (2) esophagoscopy. By these two means a diagnosis can always be made. (3) For completeness, however, it is essential that the following diagnostic steps be taken:

1. Anamnesis. A history should always be taken but never relied upon for diagnosis, negatively or positively.
2. General physical examination.
3. General examination of nose and throat, mouth and teeth. Focal infections are important.
4. Mirror examination of larynx and pyriform sinuses. Dysphagia and odynphagia may be due to tuberculous, syphilitic, cancerous or other ulcerative disease of the larynx or laryngopharynx. Recurrent paralysis often is noted in esophageal disease.
5. Systemic tests. A Bordet-Wassermann test should never be omitted. In children a von Pirquet test for tuberculosis is always advisable.
6. Fluoroscopy.
7. Fluoroscopy with an opaque mixture and capsule.
8. Roentgenogram with and without an opaque mixture.
9. Esophagoscopy.
10. Biopsy in certain cases.

Modern esophageal practice has relegated to disuse the blind passage of a bougie as unnecessary, inferential and inconclusive at best; misleading and often fatal at worst.

Esophagoscopy is a diagnostic procedure necessary in every case of esophageal disease or dysfunction, present or suspected. The day has come when it is considered unjustifiable to treat the esophagus without looking into the esophagus. In principle, it is a specular examination, but unlike other specula the esophagoscope requires a special technic that can be

acquired only by training under a teacher (Jackson, *Arch. Otolaryngol.*). Otherwise failure and fatality are inevitable. The technic is described in special works on the subject (Jackson, *Bronchoscopy and Esophagoscopy* and *Peroral Endoscopy and Laryngeal Surgery*).

Diet in Diseases of the Esophagus.—In most cases it is better to adhere strictly to liquids because lodgment of solids leads to stasis, fermentation and irritation. The secondary mucosal inflammation increases the stenosis. Intermittent stenosis, nearly always erroneously attributed to spasm, is really the lodgment of foods or curds in the narrowed lumen followed by softening and onward passage. Milk is objectionable because of the formation of obstructive curds. Unless watched, most patients with esophageal disease will drift into a diet of milk, raw eggs and meat broths. This results in acidosis and depression. An abundance of fruit juices and vegetable soups should be given; but they should be strained through a fine-meshed, wire-gauze-bottomed colander. Rectal feeding is a delusion; water may be thus supplied, but nutrition cannot be maintained.

Dehydration in Esophageal Diseases.—Most of the deaths in esophageal stenosis are due to dehydration. If not watched, more or less intermittent but prolonged shortage of water will result in death from acidosis and dehydration. Even patients on liquid diet may get short of water. It is this condition of dehydration that causes such bad statistics from gastrostomy, an operation that is almost always postponed too long. Before the operation water should be supplied by colonic drip and hypodermoclysis. Drooling of saliva in the early stages of esophageal stenosis may add to dehydration; later the flow of saliva decreases and even ceases because of the dehydration.

Pulmonary Complications in Esophageal Disease.—Diseases of the tracheobronchial tree and the lungs are very common sequelæ of esophageal disease. They may occur by direct extension, as in cancer and peptic ulcer; much more commonly they are the result of inspiration of food and secretions that overflow into the larynx because of the obstruction to normal free drainage through the esophagus. There is, between meals, normally a continuous flow of saliva through the esophagus into the stomach. This normal esophageal salivary drainage in the adult amounts to anywhere from a few teaspoonfuls to a pint or more (15 to 500 c.c.), varying according to taking of food, kind of food seen or eaten, quantity of liquids drunk, individual variation, etc. If this saliva cannot drain away freely because of esophageal obstruction, more or less overflow occurs, though the patient seldom realizes the situation and the physician is likely to overlook the fact. All the patient notices is that secretions bother him and make him cough. In many cases this seems to be noticed only at night. These secretions often contain food, but this is of little consequence compared to the fact that they are carriers of all sorts of infective agents. Under normal conditions these infective secretions rarely overflow into the

larynx, and they are quickly expelled by cilia and cough when they do. These defensive agencies are overwhelmed by inspiration of too great quantities of overflow in cases of esophageal obstruction. The infections get past the epithelial barrier and reach the lymph- or blood-channels, and pulmonary complications soon become established.

DISEASES OF THE ESOPHAGUS

The following is a categoric list of abnormal conditions found in the esophagus; they may exist alone or a number may be associated in the same patient.

1. Anomaly.
2. Stricture, congenital.
3. Esophagitis, chronic.
4. Erosion.
5. Ulcer, benign, peptic.
6. Trauma.
7. Esophagitis, acute.
8. Stricture, "spasmodic."
9. Stricture, inflammatory.
10. Stricture, cicatricial.
11. Dilatation, local.
12. Dilatation, diffuse.
13. Diverticulum.
14. Compression stenosis.
15. Mediastinal tumor.
16. Mediastinal abscess.
17. Mediastinal glandular mass.
18. Aneurysm.
19. Malignant neoplasm.
20. Benign neoplasm.
21. Tuberculosis.
22. Lues.
23. Actinomycosis.
24. Blastomycosis.
25. Varix.
26. Angioneurotic edema.
27. Serum disease.
28. Herpes.
29. Hysteria.
30. Paralysis.
31. Foreign body, (a) pharynx, (b) larynx, (c) trachea, (d) esophagus.
32. Antiperistalsis.

Anomaly.—In anomalous conditions there is usually an absence of a part of the esophagus. The portion or portions present usually communicate with the airway. This is always fatal soon after birth and gastrostomy is useless because of fatal pulmonary complications from entrance of infective secretions, of food or of both. If there is no communication with the airway the child's life may be saved by gastrostomy. The saliva, unable to drain away normally, will overflow into the larynx and be inspirated into the lungs. If kept drained by the face turned toward the pillow the child will be soon dehydrated and malnutrition from lack of saliva in the stomach (Jackson, *Arch. Pediat.*) will be inevitable. The secretions should be withdrawn from the mouth and added to the contents of the feeding funnel. When the age of six months is reached perforation by combined esophagoscopy and retrograde esophagoscopy may be done if the intervening gap between the upper and lower segments is not greater than about 3 centimeters (Jackson, *Bronchoscopy and Esophagoscopy*).

Congenital Stricture and Congenital Web.—Unlike the imperforate congenital condition described above, a congenital narrowing of the esophagus is always curable. Any sort of lumen can be increased in diameter by esophagoscopic dilatation. Success and safety depend on slow, careful and patient work. Rapid dilatation is not only dangerous but the results are not permanent. Blind methods are nearly always fatal. Esophagoscopic dilatation is safe because it is done under guidance of the eye.

Congenital diverticulum is probably atavistic in origin. It is, strictly speaking, a hypopharyngeal disease but is always classed as esophageal. It is amenable to the same treatment as the pulsion diverticulum (*q. v.*).

Spontaneous Rupture and Gangrene of the Esophagus.—These are rare diseases of unexplained etiology. The prognosis is nearly hopeless and treatment is probably useless. Shock, toxemia, hemorrhage and dehydration are to be combated by the usual means.

Trauma of the esophagus is sometimes caused by a foreign body; more often by ill-advised efforts at removal of a foreign body. In either case bismuth subnitrate dry on the tongue at frequent intervals for its local effect is antiseptic and curative, if the trauma is slight. It adheres to the traumatized areas. Instrumental trauma is usually the result of blind methods. It is usually perforative because of the very thin walls of the esophagus. Resultant subcutaneous emphysema, if cellulitis does not follow, usually requires no treatment. *Cellulitis* is usually fatal. An ice-bag to the neck is the best treatment. If pus forms it must be evacuated either endoscopically or externally, according to the direction of extension. Food should be sterile liquids, and the water should be sterile. Oral sepsis should be minimized by cleansing and dilute alcoholic mouth washes. Shock, toxemia, hemorrhage and dehydration are to be combated by the usual means. *Mediastinal emphysema* and *septic mediastinitis* are usually not amenable to treatment. *Pneumothorax* is a common result of blind instrumentation. If fluid accumulates in the pleura and needling shows the fluid to be infected, thoracotomy should be done at once; it will be necessary ultimately, and delay will mean adhesions and difficulty in obtaining efficient drainage.

Acute Esophagitis.—If due to trauma the treatment is as given under that heading. If due to *the swallowing of caustic acids or alkalies* chemical antidotes such as baking soda (sodium bicarbonate) for the acids and vinegar for the alkalies may be used, if the patient is seen at the time of the accident. Later, the burns of the mouth are so painful the child may die of dehydration unless forced to take water. The thick, viscid mucus in the mouth should be aspirated and water should be given almost continuously with a medicine dropper; it may also be given by bowel. Bismuth subnitrate dry on the tongue in small doses at frequent intervals for its local effect is the best treatment for this and all other forms of acute esophagitis.

Chronic Esophagitis.—This disease can be diagnosed only with the

esophagoscope. It is usually associated with vague, dull aching, localized subjectively at the back of the sternum and extending through to the back. This symptom is not sufficient for diagnosis but it always calls for a diagnostic esophagoscopy. The most frequent cause is stagnation of food and secretions secondary to some form of stenosis. The treatment consists in preventing stagnation and the administration of bismuth subnitrate dry on the tongue. The cause of the stagnation must be eradicated if curable; if not, the food must be continuously removed by lavage. Compression stenosis (*q. v.*) is, next to preventriculosis, the most common form of stenosis-producing esophagitis. The dietary should not include rough, irritating foods, spices, pepper, mustard and the like.

Erosions of the Esophagus.—These are occasionally seen in acute esophagitis; they are common in chronic esophagitis. The epithelium is superficially destroyed as the result of stasis and the irritation of fermented food. The eating of rough, dry or very hot foods may cause them, and the intensity of the inflammatory process is also a factor. The diagnosis can be made only with the esophagoscope. Treatment consists in the care of the accompanying chronic esophagitis as outlined above.

Ulcer of the Esophagus.—Non-specific ulcer of the esophagus usually results from contact of a caustic alkali or acid. The healing is slow because of the irritation of food; this is especially the case when there is stasis. The esophagus normally empties itself promptly; any stagnation, even of normal secretions is irritating. The treatment consists in (*a*) esophagoscopic cure of the stenosis to restore normal drainage; (*b*) esophagoscopic applications of remedies, like argyrol 10 per cent, silver nitrate 5 per cent, chlorlyptus, or gomenol; and (*c*) the administration of bismuth subnitrate dry on the tongue in small doses six or seven times daily, preferably after rather than before the intake of food or drink. The bismuth powder adheres to eroded or ulcerated surfaces.

Peptic Ulcer.—Certain characteristics justify separate consideration of this disease. Peptic ulcer occurs usually in the lower third of the thoracic esophagus; the abdominal esophagus seems almost immune and the upper esophagus entirely so. The causes are twofold. The initial ulcer is probably from an infective focus elsewhere; the perpetuating factor is probably hydrochloric acid from retrograde flow of gastric juice or from the glands in islands of gastric mucosa in the esophagus. The islands may furnish a vulnerable soil. Retrograde flow may be due to an abnormally patulous diaphragmatic pinchcock, or to abnormal retroperistalsis. Stasis of food and secretion may contribute to the etiology. Pain, usually extending through to the back and relievable by sodium bicarbonate, is characteristic. It is usually more severe than the pain of cancer. Odynphagia may be slight or absent. In appearance peptic ulcer is usually flat and covered with exudate; its base is not infiltrated and it does not usually occlude the lumen to any extent, unless of many years' duration. Healing

may leave cicatrices and these are sometimes stenotic. Unless this secondary stenosis is present peptic ulcer is not revealed by the Roentgen ray. It is a more common disease than was suspected in the preësophagoscopic days. The diagnosis is readily made with the esophagoscope and this is the only means of diagnosis.

Treatment consists in search for and eradication of infective foci in the tonsils, teeth, paranasal sinuses or elsewhere. Bismuth subnitrate, dry on the tongue in small doses at frequent intervals, is the best remedy. Silver nitrate in weak solution, not stronger than 5 per cent, applied through the esophagoscope directly to the ulcer, is the most efficient treatment. Stasis should be combated by esophagoscopic dilatation. Rough foods such as dry toast, raw fruits, and raw vegetables such as celery, lettuce, cabbage and the like should be excluded from the dietary. The retrosternal pain extending through to the back, which is often distressing, is promptly relieved by taking alkalies, usually sodium bicarbonate (Jackson, *J. Am. M. Ass.,* Chicago, Feb. 1929).

Malignant Ulcer of the Esophagus.—This may be carcinomatous, sarcomatous, endotheliomatous or agranulocytic. These are considered separately.

Spasmodic Stricture.—Spasmodic stricture of the esophagus, strictly speaking, does not exist. The esophagoscope has been the means of demonstrating that all of the diseases supposed to be spasmodic are really organic. Before the days of esophagoscopy an inferential diagnosis of spasm was made whenever the dysphagia was intermittent. The esophagoscope revealed the fact that the intermittency so common in all organic diseases, especially cancer, is due to lodgment, followed by dissolution and onward passage, of foods in the organically narrowed lumen. It is true that there are localized contractions of the esophageal wall, just as there are in the intestinal wall; but these contractions in the esophagus are never stenotic and, therefore, are not strictures, even temporarily. The disease called cardiospasm is probably never truly spasmodic as explained below (Jackson, *Am. J. M. Sc.,* May, 1925).

Cricopharyngeal Functional Stenosis; Incoördination of the Cricopharyngeal Pinchcock.—This disorder usually presents the subjective symptom of difficulty in starting the bolus of food downward. Once started the food passes into the stomach unimpeded. Regurgitation, if it occurs, is immediate, and is usually accompanied by coughing due to inspiration of food or drink. The condition was supposed to consist in a contraction, ahead of the bolus, of the circular fibers of the inferior constrictor known as the cricopharyngeus muscle; but our esophagoscopic studies have shown that the cricopharyngeal pinchcock is always tonically closed; it normally opens at the approach of the bolus. The so-called spasmodic stenosis at this level is really a failure of this muscle to relax coördinately with the contraction of the constrictors, so as to allow the bolus to pass. The dis-

order may be either primary or secondary to an organic lesion. Globus hystericus, "lump in the throat," and the sense of constriction and choking during emotion are due to spasmodic contraction of the inferior constrictor or the cricopharyngeus. These symptoms are not diagnostic; they are usual in congenital webs, and may be present in cancer of the hypopharynx and in cancer or tuberculosis of the larynx. Only direct examination can make the diagnosis. The disease, if there is no concomitant local lesion, usually disappears after a few passages of the esophagoscope (Jackson and Shallow).

Preventriculosis, Diaphragmatic Pinchcock Stenosis, Functional Hiatal Stenosis, Diffuse Dilatation of the Esophagus (so-called "Cardiospasm").—The esophagoscope has been the means of demonstrating that the stenosis in the syndrome formerly called cardiospasm is not spasmodic and is not at the cardia. It is located at the diaphragmatic hiatus and consists in failure of the tonically and normally closed diaphragmatic pinchcock to open at the approach of the bolus, as it normally should do, under the coördinate control of the Auerbach-Meissner plexus. This incoördination of the diaphragmatic pinchcock is one class of case. In another class there is a compression stenosis of the abdominal esophagus. The diagnosis is readily made with the esophagoscope (Jackson, *Laryngoscope,* St. Louis). The typical appearances are those of a mucosa macerated in stale fermenting food. It is white and has a furred coating that will not wipe away. The thoracic esophagus is dilated, often enormously. The hiatal pinchcock is usually closed but yields to gentle pressure with the esophagoscope in the same way as the normal hiatus, and permits passage of the esophagoscope through the abdominal esophagus without hindrance, into the stomach. The latter is compressed if abdominal disease is a factor in the stenosis. The compression yields to the advancing tube and the stomach is entered immediately. The Roentgen-ray examination reveals stasis of food in a dilated thoracic esophagus with a slow trickling of an opaque mixture through the abdominal esophagus into the stomach. The Roentgen-ray examination should precede the esophagoscopy. Both methods are necessary for diagnosis; they are sufficient. The blindly passed bougie is inconclusive at best; dangerous, often fatal, at worst. The treatment of preventriculosis or so-called cardiospasm is directed toward cure of food retention. The anatomic redundancy of the diffuse dilatation of the esophagus is permanent; it will, however, be symptomless if there is no retention. In cases of incoördination of the diaphragmatic pinchcock the vagus may be involved and other portions of the nervous system may be abnormal. All patients with so-called cardiospasm require a thorough neurologic examination on which to base general treatment. An abundance of rest in bed, say sixteen hours out of the twenty-four, is essential. In the patients with compression stenosis of the abdominal esophagus the advisability of abdominal exploration should be considered. Slight hypertrophy of the

liver may be the cause of the compression; gall-bladder disease is quite commonly present. Cancer of the liver or stomach, duodenal ulcer and in fact almost any abdominal disease may be causative. The treatment of these conditions obviously is fundamental in the treatment of the esophageal manifestations. Diet is of utmost importance. It is well known that the pylorus does not open promptly to permit the passage of unmasticated pieces of meat, raw vegetables, raw fruits and the like. Since I discovered that the disease called cardiospasm consists essentially in the failure of the normally closed hiatal pinchcock to open, I have been struck with the probability of a similar difficulty in the passage of pieces of ill-masticated solids through the hiatal pinchcock. Often I have removed portions of rough foods clamped tightly in the hiatal esophagus. There is an abundance of clinical evidence to show that not only rough ill-masticated foods increase the stasis in so-called cardiospasm, but that a strict diet of liquids improves the condition and affords an important adjunct to treatment. Regardless of the class of case, dilatation of the hiatal pinchcock improves the condition by lessening stasis.

Hydrostatic, Aërostatic, Esophagoscopic Dilatation of the Esophagus. —This is the safest method of treating preventriculosis. The passage of a large-sized esophagoscope through the hiatal constriction into the stomach a few times at weekly intervals is sufficient to cure milder cases. In more severe cases the esophagoscopic hydrostatic dilator is required. This nearly always affords a symptomatic cure of longer or shorter duration. The 53 centimeter, full-lumen esophagoscope is introduced into the stomach far enough that the distal end is 6 centimeters beyond the hiatal pinchcock. The hydrostatic dilator is then introduced until the tip of the distal end emerges from the esophagoscope. The latter is then withdrawn 10 centimeters, while counter-pressure on the near end of the dilator maintains the latter accurately in place. The dilatation is then accomplished either by inflation with a hand-bulb, or by connecting the rubber tube of the water bag with the pressure-gauge stand, which, in turn, is connected by rubber tubing with the water faucet. The pressure-gauge is carefully watched. Usually a pressure of 10 pounds is sufficient; 20 pounds must never be exceeded. The subjective sensations of the patient are the safest guide. Severe pain indicates danger. The safe degree of dilatation may be maintained for 10 or 20 minutes; the dilating bag is then allowed to collapse either by opening the air-release valve, or by permitting the water to escape, if water pressure is being used. The apparatus is then withdrawn. If the apparatus does not come up easily, probably all the air or the water has not escaped from the bag. In this event strong traction would be dangerous. Gentle and patient working up and down of the apparatus will release the imprisoned air or water.

Hydrostatic Dilatation by Blind Methods.—Hydrostatic dilatation is contra-indicated in the presence of ulceration and is exceedingly danger-

ous when the walls of the esophagus are weakened by cancer. It is, there-
fore, dangerous to use hydrostatic dilatation until after esophagoscopic
examination has demonstrated the absence of these diseases. There are
four methods of using a hydrostatic dilator: (1) "blind," (2) with a
string, (3) fluoroscopic, and (4) esophagoscopic. These four methods
differ in the method of placing the water bag, and in the safety of the re-
spective procedures. In the blind method the dilator is introduced by sense
of touch until the distal end is thought to have passed into the stomach.
The dilator is then withdrawn a few centimeters until the middle of the
bag is thought to be in the hiatus œsophageus. There is a mark on the
stem of the dilator; when this mark is at the upper teeth the middle
of the water bag is supposed to be at the hiatus; but this is a guide
correct only in patients with an average length of the esophagus. The dis-
tance from the upper teeth to the diaphragmatic pinchcock varies with the
vertical length of the neck and the thoracic cavity, as much as 10 cen-
timeters. For this reason the fluoroscopic method is less uncertain and
less dangerous. The position of the water bag may be verified by the fluoro-
scope. The string method is so called because a string is used as a guide
to assist in the introduction of the hydrostatic dilator past the two pinch-
cocks into the stomach. The method of swallowing the string is given
below under cicatricial stenosis. As there given the string is wanted in the
stomach for withdrawal through a gastrostomic fistula; in hydrostatic
dilatation the distal portion of the string must be far enough down in the
intestines to be held securely against withdrawal when the proximal end is
drawn taut. To be certain of this anchorage a small shot (about number 6)
is attached by means of a hole in the shot to the distal end of the string.
When this shot is in or below the ileum the proximal end of the string is
withdrawn until all the slack is taken up. Then the proximal end is
threaded through the hole in the end of the hydrostatic apparatus. The
apparatus is then passed down and placed as in the blind method. The
fluoroscope may be used for verification of the accuracy of placement of
the water bag. After the water bag is placed it is allowed to fill with faucet
water as described above under esophagoscopic dilatation. The esophago-
scopic method is the most accurate and the safest.

Dilatation of the Esophagus.—This condition may be localized or may
involve the entire thoracic esophagus. Any long-continued stenosis may
produce it, and once produced it never contracts to the normal. In cancer
of the esophagus there is usually a localized dilatation above the lesion. In
preventriculosis (so-called "cardiospasm") of long standing an enormous
dilatation of the thoracic esophagus results. The only treatment necessary
for a dilatation of the esophagus is that of the subjacent stenosis. Once this
is cured the patient becomes symptom-free; the anatomic dilatation re-
mains but does not call for treatment. Much may be done to prevent dila-

tation by regulation of the diet to prevent lodgment of food and by esophageal lavage.

Cicatricial Stenosis of the Esophagus.—Scar tissue anywhere in the body usually undergoes more or less contraction during a long period of time. In tubular structures the contraction results in stricture of the lumen. The usual causes of scar tissue in the esophagus are the following: the swallowing of caustic alkalies and acids, peptic ulcer, tuberculosis, suppurating glands, syphilis, typhoid fever, diphtheria, foreign body, instrumental trauma, chronic esophagitis. The most common cause is the swallowing of household lye which is to be found in almost every kitchen. The fact that it is a powerful corrosive poison is rarely realized; it looks like sugar and it is carelessly left within reach of children. The stricture may be a single web-like structure on one side only or it may be annular; it may be isolated or multiple, it may be in form of an excentric series, or it may be a continuous mass of scar tissue. The lumen may be obliterated and the esophagus converted into a cord, constituting a total atresia.

Only two methods of diagnosis are safe and certain: Roentgen-ray examination with an opaque mixture, and direct inspection with the esophagoscope; both should be used.

Patients with esophageal obstruction are, as previously mentioned, prone to pulmonary complications because of inspiration through the larynx of the overflowing secretions that normally drain into the stomach through the esophagus. These complications are particularly common in cicatricial stricture. Apart from this the prognosis under treatment is good, if total atresia is prevented.

Treatment.—All rapid methods and all blind methods of treating this form of esophageal stricture are attended with high mortality; slow methods are not only safer but the results ultimately obtained are permanent. Two methods are safe and practically always successful; they are esophagoscopic dilatation and retrograde dilatation.

Esophagoscopic dilatation is carried out under the guidance of the eye. The lumen of the stricture is found with the esophagoscope and the dilators are gently insinuated in a series of increasing sizes. Web-like strictures permanently disappear after a few treatments; strictures involving the entire periphery of the esophageal wall, if annular, require a somewhat longer time; if very extensive up and down the esophagus a long time may be required.

Retrograde dilatation requires a gastrostomy. The patient swallows one end of a string (Piersol's braided silk No. 4½) which is supplied from a spool in the pocket continuously as the distal end goes down. The taking of fluids does not interfere and in fact helps wash the string downward. When it has bridged across the stomach to the pylorus the bight of the string is "fished" out of the gastrostomic fistula. The retrograde bougie is then attached to the string by its loop and drawn upward. The string is

renewed at each sitting by attaching a new string to the old one, making it "endless" by bringing the upper end out of the nose and attaching it to the end remaining out of the gastrostomic fistula. The sizes of the retrograde bougies are slowly increased at subsequent sittings as dilatation warrants. The safety of the method depends on the anatomical fact that below the stenosis there is a smooth inverted conical approach to the lumen of the stricture, whereas the esophagus above the stricture is usually a mass of folds and pockets that trap the point of a blindly passed or string-guided bougie and lead to fatal perforation.

Impending Atresia.—If total atresia threatens, gastrostomy should be done at once and a string should be swallowed immediately. It is easy and safe by the methods mentioned to dilate any sort of lumen, even though it be a mere fistulous tract; but if the lumen becomes totally obliterated, perforation to get a start is extremely dangerous. Whatever may be said of gastrostomy for cancerous stenosis, it is always indicated in cicatricial stenosis of small lumen. It enables a safe cure by retrograde dilatation. The remarks on diet and dehydration given in a previous paragraph are important in the care of patients with cicatricial stenosis.

Atresia of the Esophagus.—If the total obliteration of the esophageal lumen has not been averted by the means hereinbefore mentioned, it may be possible to perforate the atresic portion by combined peroral and retrograde esophagoscopy.

Diverticulum of the Esophagus.—There are three distinct types of this disease, congenital, pulsion and traction, so named from supposed etiologic factors.

Congenital diverticulum of the esophagus is atavistic. It is rare as a distinguishable anomaly, but a congenital factor may be initial in the etiology of the pulsion or the so-called traction diverticula. Most often it is located in the pharynx, but occurs in the cervical and thoracic portions of the esophagus. It requires removal except when it springs from the thoracic esophagus.

Pulsion Diverticulum of the Hypopharynx or Esophagus (Pharyngeal Pouch).—This is a hernia of the hypopharyngeal wall out through a muscular cleavage, where external support of the loose elastic wall is lacking. It is usually considered as an esophageal disease, though anatomically it is pharyngeal in the location of its mouth. It is caused by the failure of the cricopharyngeal pinchcock to open at the approach of the bolus, in the coördinate deglutitory cycle. Pressure of the food forced downward by the inferior constrictor brings undue pressure on the hypopharyngeal wall which herniates out through the weak point in the external support. The weak point may be between the oblique and orbicular fibers of the cricopharyngeus or between the fibers of the latter muscles. A congenital factor may exist here. A vicious circle is sooner or later created because the increased difficulty in swallowing results in increased pressure.

Hasty gluttonous eating and the inefficiency of mastication resulting from haste, poor teeth or artificial dentures are important factors. It occurs usually in elderly people.

The chief symptoms are a gurgling sound on swallowing, dysphagia and the bringing back of food swallowed some minutes or hours before. The sound and the difficulty in swallowing may be so embarrassing that the patient prefers to eat alone.

The diagnosis is made by Roentgen-ray examination and esophagoscopy; both are required for certainty.

Treatment may be palliative or curative. Palliative treatment is indicated only in patients who refuse operation. It consists in washing out and downward of the retained food by the slow swallowing of one or two glassfuls of water after each meal. If necessary less water may be taken during the meal to allow of taking the necessary amount afterward for lavage.

Operation is the only curative method known, though there are a number of operative procedures. Anchoring the sac bottom upward involves the least operative risk; but recurrence of the annoying symptoms is frequent. Excision of the sac may be divided into a two-stage operation; but the best results have been obtained by a single stage excision of the sac by the surgeon working through an incision in the neck assisted by an esophagoscopist working endoscopically. This is known as the Gaub-Jackson operation.

Traction Diverticulum.—This is usually located in the thoracic esophagus and is due to the pocketing or pouching of the esophageal wall by the cicatricial contraction following periesophageal suppurative foci, most often glandular. The diagnosis is made by Roentgen-ray examination and esophagoscopy. This form of diverticulum, if there is no stenosis below it, may be free from the annoying symptoms of pulsion diverticulum; or there may be retention and regurgitation of stale food; in either case no treatment other than lavage as noted above, is required. If, before cicatrizing, the suppurative focus has burst through the esophageal wall, stricture will result and give rise to dysphagia and stasis of food. Esophagoscopic dilatation of the stricture will cure the stenosis and thus free the patient from the annoyance of stasis of food in the diverticulum.

Compression Stenosis of the Esophagus.—Difficulty in swallowing and stasis of food with subsequent esophagitis may result from compression of the esophagus by any periesophageal mass, such as *goiter, aneurysm, mediastinal abscess, intrathoracic tumor, adenopathy, benign or malignant neoplasm, or cardiac hypertrophy,* especially of the left auricle. The treatment is that of the lesion producing the compression. If this is incurable, relief may be obtained by esophageal dilatation to push away the compressive mass. In severe cases *esophageal intubation* may be indicated. This is accomplished by the esophagoscopic placement of an esophageal intubation tube. A Jutte duodenal tube may be used temporarily.

Carcinoma and Sarcoma of the Esophagus.—Sarcoma is rare, but cancer is common. Sudden or intermittent dysphagia is the chief symptom. The patient may have slight vague symptoms that are ignored by him or his physician. These symptoms are only too often dismissed from consideration under the erroneous diagnosis of *globus hystericus*. When the growth gets large enough to encroach on the esophageal lumen an unusually large or ill-masticated bolus may lodge. This sudden onset may mislead the diagnostician who infers that cancerous obstruction could not appear suddenly. The lodged bolus soon softens and goes on into the stomach; then a second erroneous inference is often the diagnosis of spasmodic stenosis. Practically all patients coming to the bronchoscopic clinic give a history of having had an erroneous diagnosis of spasm made at some time in the course of their disease. There are only two methods of diagnosis that are certain and safe; they are the Roentgen ray and esophagoscopy. They are sufficient; both are necessary. Direct inspection with the esophagoscope not only permits ocular examination of the lesion but a specimen for biopsy may be taken.

Treatment is chiefly palliative. The esophagoscopic implantation of radon emanation "seeds" may arrest the progress of the growth for a varying length of time. The Roentgen ray often delays the progress of the growth. Gastrostomy, if done early, prevents the emaciation of the patient and improves the swallowing greatly by putting the esophagus at rest and stopping the irritation of retained foods that ferment. Only water is given by mouth to cleanse the growth. All criticisms against gastrostomy are based upon operations done too late. If, however, the patient refuses operation the growth may be dilated esophagoscopically or an esophageal tube may be placed esophagoscopically. Diet is of the utmost importance; suggestions as to this are given above. The suggestions given under the heading of dehydration are also of importance.

Agranulocytosis of the Esophagus.—This rare lesion has been observed in the postcricoidal region in almost all cases associated with a similar lesion of the pharynx. The diagnosis is by histologic examination of a specimen removed esophagoscopically and considered in connection with a blood examination showing a progressive decrease in the leukocytes and granulocytes.

Benign Neoplasms of the Esophagus.—These are not common. Papilloma, lymphoma, fibroma, myoma, cyst, granuloma, edematous polypus and angioma are the least uncommon. The chief symptom is dysphagia. The diagnosis can be made only with the esophagoscope; and this instrument affords the only means of removal. The prognosis as to removal is good and the growths rarely recur.

Tuberculosis of the Esophagus.—The lesion may be a diffuse superficial erosive type of ulcer, or it may be a deeper type of ulceration from the perforation of an adenopathic suppuration. The diagnosis can be made

only with the esophagoscope. The treatment is general rather than local unless there is stenosis. For this esophagoscopic dilatation is safe and curative.

Syphilis of the Esophagus.—Gumma is the form in which syphilis is least uncommon in the esophagus. As elsewhere it is followed by suppuration. The diagnosis is made by esophagoscopy and the Bordet-Wassermann tests; both are necessary. The treatment is that of the systemic infection. Healing of the ulceration is almost always followed by cicatrices which require esophagoscopic dilatation. Neglect of esophagoscopic treatment of the stricture may result in total atresia as mentioned under cicatricial stricture.

Blastomycosis of the Esophagus.—This form of mycosis produces an infiltrative and ulcerative stenosis of the esophagus the character of which can be determined only by the esophagoscopic removal of a specimen. The disease can be cured by the internal administration of potassium iodid gradually increased from very small up to full dosage. Stenosis is to be treated by esophagoscopic dilatation. The prognosis is good unless the esophageal disease is complicated by pulmonary blastomycosis. The latter is much less amenable to treatment than the esophageal lesion.

Actinomycosis of the Esophagus.—This disease is similar to blastomycosis in the same region except that it is not amenable to curative treatment. The stenosis can, of course, be successfully dealt with by esophagoscopic dilatation.

Esophageal Varix.—Varicosities occurring in the esophagus are usually at the lower end. Dysphagia and hematemesis may be present or absent. Slow, continuous blood-loss here may be the cause of an otherwise unexplained anemia. The diagnosis can be made only with the esophagoscope. The bleeding can nearly always be arrested by the administration of small doses (about 1 gram) of bismuth subnitrate given dry on the tongue every few hours. Careful regulation of the diet, as indicated above, is necessary for local reasons. Abdominal disease [1] should always be thoroughly searched for and, when found, treated according to indications.

Angioneurotic Edema, Urticaria, Serum Disease, and Herpes of the Esophagus.—These are rare lesions of the esophageal mucosa; but perhaps not so rare as the literature would indicate. Their affinities may preclude differential diagnosis, and they may be essentially the same; but there is no difficulty in distinguishing them from other lesions of the esophagus by means of the esophagoscope. It is the only means by which the diagnosis can be made with certainty. Herpes is distinguished by blisters or blebs that soon break, leaving a raw eroded surface which is later covered with exudate. The esophageal lesions may accompany or alternate with similar lesions elsewhere. The general manifestations may be those of herpes simplex or herpes zoster. Angioneurotic edema,

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[1] Especially cirrhosis of the liver.—Editor.

urticaria and serum disease are associated with other similar manifestations. The treatment should be both general and local. The general treatment (q. v.) is directed toward prevention of recurrence and is the more important in most cases because of the self-limited duration of the lesions. There are a few cases, however, in which the lesions may become chronic unless terminated by treatment. Chronic edema may succeed the angioneurotic lesion; this calls for treatment by bismuth subnitrate as mentioned below. Dehydration must be guarded against if the dysphagia is great. Continuous drip by bowel is the most efficient way of getting water into the body. The eroded surface left by the acute herpetic lesion may drift into chronic ulcer. This is particularly true of herpes of the lower end of the esophagus; in this location the ulcer may assume the character of peptic ulcer (q. v.). Two means are of value in preventing this. Bismuth subnitrate in small doses given dry on the tongue at frequent intervals will adhere to the eroded surfaces and is usually effective. If the discomfort back of the sternum or in the epigastric region persists, chronic ulcer is impending and esophagoscopic applications of silver nitrate in weak solution (about 5 per cent) are called for.

In serum disease the dermal urticaria, the toxic and other phases of the serum reaction are so distressing that the presence of a reaction in the esophageal mucosa is usually overlooked. If the dysphagia threatens dehydration, water must be continuously given by bowel.

Globus Hystericus and Hysteria of the Esophagus.—The common complaint of "a lump in the throat" or other and less clear statements of subjective sensations are not imaginative as formerly supposed. They are due to contractions of the inferior constrictor muscles. The treatment is neurological, including rest, exercise, diversion to eliminate morbid introspection, elimination of social activities, candy, tobacco and alcohol. It cannot be too emphatically stated, however, that the diagnosis of hysteria of the esophagus should never be made until organic disease has been eliminated by the Roentgen ray and the esophagoscope. Almost all cases of cancer and other serious diseases of the esophagus are mistakenly diagnosed *globus hystericus* at some stage as shown by the histories of patients coming to the bronchoscopic clinics.

Paralysis of the Esophagus.—Broadly considered, there are two active factors in the swallowing function: (1) The bolus is squeezed past the coördinately opened cricopharyngeal pinchcock by the contraction of the constrictor muscles of the pharynx. (2) The bolus is carried downward by the contractions of the muscular coat of the esophagus. Paralysis may affect either or both of these muscular systems. Gravity is of little assistance and alone cannot carry food or drink to the stomach. A normal person can swallow "up hill," as in drinking from the pool of a spring, but a person whose esophagus is paralyzed cannot swallow in the erect posture by gravity alone, though his esophagus is free from stenosis. Esophageal paralysis is

usually bulbar, but may be peripheral. It is a common symptom in myasthenia gravis, bulbar palsy, syringomyelia, encephalitis, cerebellar tumor or abscess, and in the syndrome of Avellis. It may be toxic, as in diphtheria, botulism and plumbism. The diagnosis can be made positively only with the esophagoscope; but it may be suspected when a stomach tube can be readily passed all the way into the stomach of a patient who cannot swallow anything. Before drawing such an inference it is necessary to be certain that the patient has made genuine efforts to swallow and that the stomach tube really reached the stomach.

The prognosis and the treatment are those of the associated general disease. To the treatment must be added the use of the stomach tube in feeding. There is no need of gastrostomy or of wearing a duodenal tube. The ordinary stomach tube can be readily passed by the nurse for each feeding.

Antiperistalsis.—In this disease the patient usually complains of a subjective sensation of food rising into the esophagus from the stomach; occasionally, it comes from the mouth. There may be no food rise at all; the sensations may be from the muscular contractions of the stomach and esophagus. The antiperistaltic movements may be rendered visible in the fluoroscope by the swallowing of an opaque mixture. Esophagoscopy is necessary to rule out organic disease. The usual cause is abnormality in the gastro-intestinal tract, especially colonic stasis. Treatment is based on the finding. Very gentle laxatives continuously given are usually curative in the toxic cases. Hypercatharsis is especially to be avoided.

Foreign Body in the Esophagus.—The symptomatology and diagnosis are given on page 84, in Volume V. There is only one method of treatment worthy of a moment's consideration, namely, esophagoscopic removal under guidance of the eye. The statistics of the bronchoscopic clinic show that any foreign body that has gone down the natural passages can be removed esophagoscopically by the same route. The procedure is highly technical and requires prolonged special training. Safety-pins lodged point upward may require closure before they can be safely removed; other foreign bodies, as for instance artificial dentures, may require version.

Foreign Bodies in the Stomach.—A foreign body may escape from the esophagus into the stomach. If it is of a character dangerous to allow to pass through, as, for instance, an open safety-pin or a capsule containing radium, it may be removed through the mouth by gastroscopy. If deemed advisable to allow it to pass on, peristalsis should not be accelerated by a cathartic or a change of diet. The most favorable conditions for passage are normal gastro-intestinal contents and movements. If the pylorus is abnormally small, peroral gastroscopy may be indicated even though the foreign body be not of a character rendering intestinal passage hazardous. The size of the pylorus is to be determined by the roentgenologist.

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CHAPTER LIII

THE TREATMENT OF NEPHRITIS

John P. Peters

In the present unsatisfactory state of our knowledge of the etiology and pathogenesis of the nephritides, treatment must be almost entirely symptomatic, depending less upon the essential nature of the disease than upon its functional manifestations.

Therapeutic measures can, in a general way, be classified according to their purpose into:

1. Those directed toward the removal of the cause of nephritis.
2. Measures directed toward the relief of renal insufficiency.
3. Measures directed toward the relief of renal edema.
4. Measures directed toward the relief of circulatory disturbances.
5. Measures directed toward the relief of other secondary symptoms such as anemia.

The relative importance of one or the other type of therapy bears some relation to the nature of the renal condition under consideration. However, there are so many cases that cannot be placed in any exact category that attempts to discuss treatment according to any given classification of renal disease, involves unnecessary repetition. Renal insufficiency, in the sense in which it will be employed in this chapter, and circulatory disturbances are most often observed in the latter stages of arteriosclerosis of the kidneys, in the latter stages of glomerular nephritis and in severe cases of acute nephritis. These are the conditions, also, in which both hypertension and the symptoms usually called uremic, occur with greatest frequency, but in which one rarely encounters renal edema. The latter occurs most characteristically in acute nephritis, in the earlier or milder forms of glomerular nephritis and in the so-called nephroses. The focal nephritides, for the most part of embolic origin, usually cause renal insufficiency without producing either hypertension or renal edema (Volhard).

Therapeutic measures directed toward the elimination of etiological factors may be dismissed with few words, because so little is known of the causes of any of the types of nephritis. Recent studies have tended to prove that in most instances acute glomerular nephritis and its chronic sequelæ are the remote local effects of infections with pathogenic streptococci, usually hemolytic, of the types that produce toxins (Longcope and collabora-

tors). It is to be hoped that the general early use of scarlet fever antitoxic serum will reduce the incidence of the septic complications of this disease and the nephritis that so often accompanies them. As nephritis usually occurs after the acute manifestations of scarlet fever have subsided and when there is an excess of antitoxin in the body, it is hard to believe that it is due to the specific toxin of the disease. Antitoxic serum can, therefore, hardly be expected to have any beneficial influence after the disease has developed. The proper treatment—with surgical drainage, if necessary —of septic foci after scarlet fever and other streptococcus infections is advisable. In the author's experience, the removal of tonsils and other similar procedures that involve denudation of healthy tissue, during the active inflammatory stages of the disease, are not wise. They may provoke an exacerbation of the nephritis. If an individual who is subject to frequent sore throats, develops acute nephritis after tonsillitis, the latter should receive the treatment it would be accorded in the absence of renal complications. After the acute inflammation has subsided, the tonsils may well be removed as a prophylactic measure against future recurrences. The indiscriminate removal of tonsils, teeth and other organs, in the absence of definite history or evidences of infection, can hardly be justified. Often enough surgical removal of all dispensable infective foci is without apparent influence. The organisms responsible for the disease seem to establish themselves, usually in the pharynx or nasopharynx, in an inaccessible manner. Removal of presumptive foci in these cases may merely afford new opportunities for acute invasion with consequent exacerbation, sometimes fatal, of the existing nephritis. In advanced chronic nephritis especially with evidences of renal insufficiency, surgery is warranted only if there are clearly positive indications. In this condition the kidney has been irreparably damaged, and the best that can be hoped is the subsidence of active inflammatory processes and replacement by scar tissue. The reserve power of the organs is so far reduced that they may not stand the additional burden thrown on them by operation, even if the latter does not result in renewed infection.

The term nephrosis, as used by Volhard, Epstein and others, should be considered only as a useful descriptive appellation for a certain symptom-complex. This symptom-complex in its purest form may be found in the course of glomerular nephritis (Peters and collaborators). It is also the characteristic picture observed in amyloid disease (Volhard and Fahr, Peters and collaborators). The presence of a nephrotic syndrome of insidious development should lead, therefore, to a careful search not only for streptococcus infections but also for tuberculosis and chronic suppurative processes of other kinds. It is also important to distinguish between glomerular and focal nephritides. In the latter the bacteria themselves are located in the kidneys, which are the site of embolic abscesses, and can be recovered in the urine. The urine in true glomerular nephritis is sterile.

From the standpoint of prognosis and therapy bacteriological study of the urine should be more commonly and carefully practiced.

Pictures quite comparable to those of nephritis are found in and after pregnancy toxemias. The early termination of pregnancy, when such conditions first present, and the avoidance of subsequent pregnancies, if any vestiges of the toxemia persist, are the only means at present available for the prevention of the chronic renal and vascular diseases that develop if the toxemias are allowed to run their course.

SYMPTOMATIC TREATMENT

Symptomatic measures, whether directed toward the relief of renal insufficiency, renal edema, circulatory disturbances or other symptoms, consist chiefly in (1) regulation of the food constituents of the diet; protein, fat and carbohydrate; (2) regulation of the intake of water and salt; (3) medicinal and miscellaneous therapeutic measures.

Measures Directed towards the Relief of Renal Insufficiency

It has been demonstrated repeatedly that destruction of renal substance as a whole causes consistently but one detectable functional disturbance which is loss of the ability to excrete a concentrated urine, hyposthenuria. For this reason Volhard and others recognize this phenomenon only as evidence of renal insufficiency *per se*. Proof of the existence of hyposthenuria is the maintenance of a low urinary specific gravity in spite of spontaneous or extraneous efforts well directed towards the production of conditions which compel the excretion of a concentrated urine. These conditions have been defined most accurately by Addis and his associates. Concentration tests have too far fallen into disuse. If they are properly conducted they give information of a more specific nature than any that can be secured by other procedures.

Regulation of the Fluid Intake.—The effects of hyposthenuria are evidenced especially in the excretion of the nitrogenous waste products of protein metabolism, and in the accumulation of these substances, especially urea, in the blood. Such accumulations do not usually occur, however, until kidney destruction has reached such an advanced stage that compensation can no longer be maintained by the production of polyuria. The latter is the normal adaptive reaction to loss of concentrating powers and should, therefore, be supported by therapeutic measures.

Patients with renal insufficiency *must* pass large quantities of urine. To accomplish this they must receive adequate quantities of fluid. Fatal uremia is rarely encountered in patients who void as much as 2000 c.c. of urine daily, unless the protein metabolism is unduly high by reason of injudicious diet or some complicating condition, especially febrile dis-

eases. It is impossible to generalize about the amounts of fluid that should be given. It is not the fluid intake, but the urine volume that is important. The former is only sufficient if the latter is adequate, not less, preferably more, than 2000 c.c. in the severe stages of the disease; in the earlier stages enough to maintain the blood non-protein nitrogen at or near the normal level, with the diet properly regulated.

With the exception of some types of acute nephritis, the renal diseases which cause hyposthenuria, are seldom attended by renal edema. When edema appears in such diseases, it is almost always a sign of heart failure resulting from hypertension and arteriosclerotic heart disease. Restriction of fluids, in these circumstances, is of questionable value and should not be carried to an extreme. If circulatory compensation cannot be secured by other measures, especially rest and digitalis, a favorable outcome is not to be expected. Edema in these cases is not, in itself, a serious symptom; it is important only as an indication that circulatory failure has interfered with urine excretion. Its elimination is of no value unless it is accomplished by diuresis. The edema fluids presumably contain the toxic substances the excretion of which is required. If the rate of excretion of these substances does not keep pace with the rate of water elimination, as it may not in hyposthenuria, they must become concentrated in the body. The precipitate appearance of uremia after diuresis has been frequently reported, and may well be due to the fact that the diuresis has carried out water in excess of toxic solutes. To guard against this an adequate supply of water must be available. It is seldom advisable to limit fluids to less than 2000 to 2500 c.c. in the presence of advanced renal insufficiency. Certainly enough fluid should always be given to compensate for the loss of water by extra-renal channels.

Attempts to make other excretory channels, such as the gut and the sweat-glands, assume the functions of the kidney have been largely abandoned. Feces, vomitus, sweat, and the respiratory air are important channels for the elimination of water. The first three may also contain considerable amounts of salts. Even when the non-protein nitrogen of the blood is extremely high, the same excreta contain only small quantities of nitrogen. To make them serve vicariously for the kidneys, leads to the diversion of fluid from the latter to no purpose. The most seriously damaged nephritic kidney seems to be a more efficient organ for the excretion of nitrogen than the healthiest gut or skin.

Dietary Regulation.—One may well ask why so much emphasis is laid upon the necessity of eliminating nitrogenous waste products when there is no evidence that the latter are injurious. For the excretion of the waste products of the metabolism of carbohydrate and fat, and even for the elimination of salts, other channels than the kidney may serve. For the excretion of protein waste products, and especially those that contain nitrogen, on the other hand, the body is almost entirely dependent upon

the kidney. Therefore, although it is reasonably certain that none of the well-recognized non-protein compounds is responsible for uremia, it is fair to assume that the substances that are responsible are protein derivatives. The retention of non-protein nitrogen indicates the inability of the organism, under given circumstances, to excrete the known protein waste products at a sufficiently rapid rate, from which fact it is inferred that other waste products are also being retained. The inference seems to be roughly justified by the facts, at least in renal disease; because a high degree of nitrogen retention usually indicates a bad prognosis and is almost always found in uremia.

Nitrogen retention of purely renal origin is found only when there is true renal insufficiency. There is, therefore, no clear reason except tradition for employing measures to combat such retention unless hyposthenuria can be demonstrated. It must be clearly recognized that high blood non-protein is not in itself pathognomonic of renal insufficiency. The level of the blood non-protein nitrogen is dependent upon several factors, of which the excretory capacity of the kidney is but one; the other chief factors are the rate of protein catabolism, the amount of water available for excretion by the kidney, and the state of the circulation. In pneumonia, for example, nitrogen retention is commonly observed without other evidence of serious renal damage because an extreme degree of toxic destruction of protein is coupled with oliguria and often faulty circulation. In obstruction of the alimentary tract similar factors have an even more striking effect. Congestive heart failure, resulting, as it does, in oliguria, may cause the non-protein nitrogen to rise to extreme heights when the kidney is but little damaged.

It follows, obviously, that the proper treatment of nitrogen retention does not consist only in limiting the protein of the food. It must be supplemented by measures that insure to the kidneys an adequate supply of fluid available for excretion, and an efficient circulation. These latter measures have been discussed above. It is too little appreciated in practice that restriction of dietary protein does not insure reduction of protein catabolism and that the latter alone is of any benefit in combating nitrogen retention. It must be borne in mind that patients do not necessarily use diets prescribed for them. If such diets are deficient the subjects supplement them with food taken from their own tissues. Nephritis with renal insufficiency is usually both a chronic disease and a wasting disease (Peters). Diets must, therefore, be so regulated that they can be used for long periods without danger of malnutrition.

It is usually stated that the average normal individual requires two-thirds of a gram of protein per kilogram of body weight per day as a minimum for subsistence. Such minima are only attained, however, if care is taken to provide sufficient calories in fat and carbohydrate to meet his energy requirements. It is too often assumed that subjects with

diseases of all kinds can subsist on just as little protein without special attention to caloric requirements. One finds recommended for nephritic patients in standard texts diets containing only 40 grams of protein and 2000 calories, although such diets can hardly fail to promote wasting. One gram of protein per kilogram per day probably represents a safe minimum for prolonged use. Besides this sufficient fat and carbohydrate should be given to maintain the body weight at the optimum normal standard. An adult leading a life of average activity needs not less than 40 to 50 calories per kilogram and usually more. No extra protein need be added on account of physical activity, provided the ration of fat and carbohydrate is large enough. The body weight is the best criterion for the adjustment of calories.

The nature of the protein is of minor importance. It is probably advisable to give more than half in the form of animal protein because the vegetable proteins can be used less efficiently. Carbohydrate and fat should be so apportioned as to make the diet well-balanced and appetizing. It is unnecessary to say that simple and easily digestible foods are to be preferred. This does not mean that the diet need be tasteless or monotonous. Nephritic patients are far more prone to eat too little than to eat too much. Anorexia is a striking symptom in all stages of the disease. A reasonable amount of seasoning, the greatest possible variety, and careful attention to the tastes and caprices of the patient are, therefore, essential.

Sansum and Blatherwick as well as others have suggested the use of diets that provide an alkaline ash to prevent the acidosis that so often occurs in advanced stages of the disease. Whether this really possesses any special advantages remains to be proved.

In the terminal stages of the disease, or during acute exacerbations, it may be necessary to attempt to reduce protein catabolism to a still lower level, even at the expense of nutrition. This can be best effected by reducing dietary protein to an absolute minimum, while feeding large amounts of fat and carbohydrate. Diets of this nature have been recommended and employed (Goodall, Smith and Millard) to a limited extent. They are, however, so uninteresting, if not actually unpalatable, that their use is seldom practicable.

Vomiting is the symptom which most frequently defeats all efforts to supply fluids or food, and must be combated in every possible way. If the oral administration of both food and fluids is absolutely impossible, at least sufficient fluid and carbohydrate should be given by parenteral routes to prevent dehydration and starvation acidosis and to mitigate the destruction of protein which attends these states. A moderate amount of water can be introduced by retention enemas. Carbohydrate and salt can be better given parenterally with more certainty that they will be retained; they should be used in the form of 5 per cent glucose solution and normal saline, and given subcutaneously.

Regulation of Salt Intake.—In patients with frank renal insufficiency there seems to be little reason for restricting salt. In the more advanced stages of the condition it has long been recognized that the concentrations of chlorid and base in the serum are usually low, rather than high (Hartmann, Peters and collaborators). Unless it be assumed that this salt deficiency is a beneficial adaptive reaction, then strict limitation of salt is contra-indicated because it can only exaggerate the deficiency, especially if high fluids are given. Those for whom tradition weighs heavier than such ascertained facts, may find a more cogent reason for permitting salt in the fact that it makes the administration of large amounts of fluid far easier. In the comparatively asymptomatic stages of the disease 5 to 10 grams of sodium chlorid per day, the amount obtained if no salt is added to ordinarily seasoned food at the table, is usually an adequate and not excessive ration. If vomiting becomes a serious symptom, larger amounts may be required and should be given subcutaneously, if necessary, to replace that lost on account of emesis. Without a sufficient supply of salt the tissues will not retain water or cannot retain it without serious disturbances. Dehydration, a serious result of vomiting, cannot be overcome by water alone. Vomiting causes salt depletion not only by means of the salt lost in the vomitus, but also because it interferes with the ingestion of salt.

If edema develops as a result of heart failure, it may be necessary to limit salt temporarily. However, restriction of salt seems to be less efficacious than it is in edema from other causes. Explanations for this may lie in the fact that even in the presence of edema the concentration of salt in the blood-serum is usually subnormal.

There is no *drug therapy* for renal insufficiency *per se*. Drugs may be used for the treatment of symptoms such as heart failure, vomiting, etc., that exaggerate the consequences of renal insufficiency. Diuretic drugs of all kinds with the exception of digitalis (in the presence of heart failure), have been proven useless if not harmful (Christian and collaborators).

Measures Directed toward the Relief of Renal Edema

According to present theories the term "renal edema" is a misnomer; it will, however, continue to serve to distinguish, in nephritis, the edemas of non-cardiac origin from those due to heart failure. Renal edema is commonly observed in acute nephritis, in the earlier stages of glomerular nephritis and in the so-called "nephroses." It seldom occurs in patients with chronic scarred kidneys and renal insufficiency and may, indeed, give way to polyuria in progressive glomerular nephritis when hyposthenuria appears. It is usually associated with profuse albuminuria and certain definite changes in the chemical composition of the serum—increase of the free fat and cholesterol of the blood, and diminution of the serum proteins,

especially the albumin fraction. Govaerts, Schade and Claussen, and others consider that reduction of the serum proteins promotes the production of edema by lowering the colloid osmotic pressure of the serum, which ordinarily resists the tendency of the blood-pressure to force fluid from the blood-vessels to the tissues. Although there is no exact serum protein concentration at which edema consistently appears or disappears, the tendency to edema (*Ödembereitschaft*), seems to bear a rough inverse relation to the level of the serum proteins (Linder, Lundegaard, Van Slyke, Peters and collaborators. The conditions in which renal edema occurs are seldom attended by hypertension or by nitrogen retention.

Dietary Regulation.—Investigations in the author's laboratory have demonstrated that in protein starvation (malnutrition) the serum proteins are regularly found low. Furthermore, such conditions may be accompanied by edema. Finally, patients with renal edema and low serum proteins regularly present evidences of protein starvation (the ability to store large amounts of nitrogen as protein in the body). The edema lends a specious well-fed appearance which masks the malnutrition. The factors which contribute to the protein deficiency, appear to be toxic destruction of protein in the more active stages of the disease, aided by anorexia and digestive disturbances, albuminuria, and too often misguided dietary restrictions.

As patients with renal edema seldom exhibit any serious tendency to retain nitrogenous waste products, restriction of protein is not indicated; on the contrary, a liberal protein ration is required to combat the wasting which is characteristic of the disease. Moreover, if the excess protein is not destroyed, but used for restoration of tissue, it can throw no excretory burden on the kidney. The most conservative diet should afford, over and above the basic, one gram of protein per kilogram of body weight, enough to replace gram per gram the amount lost in the urine as albumin (this has served no useful purpose of metabolism), and, in addition, at least 10 grams to replace lost tissue. For a 70-kilogram man excreting daily 10 grams of albumin in the urine, 90 grams of protein is a moderate ration. More than this may be efficiently used by some subjects, but how much more is uncertain. As dietary protein is raised above a certain point, smaller amounts of each increment can be retained for tissue replacement. It is doubtful whether much is to be gained by giving more than 30 grams of protein a day in excess of the basal requirements plus the allowance for albuminuria. The unbalanced diets advocated by Epstein for nephrosis patients, although undoubtedly superior to the low protein diets generally employed, seem to the author to err in the opposite direction.

It was demonstrated by von Hösslin in the study of war edema, that high calorie diets low in protein were ineffectual in the treatment of malnutrition. High protein can, however, be used with the greatest efficiency for growth or restoration of tissue only when the energy requirements of the

individual are adequately covered by fat and carbohydrate. Diets in renal edema should, therefore, be not high in protein only but also in calories. Because of the lipemia mentioned above, Epstein advocates restriction of dietary fat. As there is no evidence that the lipemia betokens any inability to metabolize fat, and as limitation of this article of food makes high calorie feeding difficult, the author has preferred to insure adequate calories to the doubtful benefits that might accrue from restricting fat. To state the caloric requirements in actual figures is difficult. For an adult 50 calories per kilogram is seldom enough and usually too little. The aim should be to restore the patient, free from edema, to the proper normal weight for an individual of his age and stature.

In febrile stages and exacerbations of nephritis, anorexia and digestive disturbances are common and make high feeding difficult if not impossible, while rendering it all the more imperative. In these states all the usual measures to combat the digestive disturbances must be employed, and every effort must be made to stimulate appetite and to introduce the required amount of food with special emphasis on protein. Frequent small feedings are often better tolerated than the usual three meals a day.

Regulation of Fluid and Salt in the Diet.—Seldom does the concentration of chlorid or sodium in the serum of patients with renal edema diverge greatly from the normal. High chlorid is more common than high sodium (Peters and collaborators, Marrack). There seems to be a serious impairment of the ability to eliminate chlorid in the urine and difficulty also in the excretion of sodium and water. In practice restriction of sodium chlorid in the diet is the most important single measure in the treatment of edema and increases the effectiveness of all other diuretic measures. As long as edema persists, sodium chlorid must be kept at a minimum. The best means for effecting this end have been well presented by Allen. Not only must the addition to the food of salt at the table or the ingestion of specially salty foods be forbidden; but no salt must be used in the preparation of the diet, and dietary constituents that contain more than minimal amounts of salt must be avoided or used sparingly. With these precautions even a high calorie high protein diet should contain not more than 2 grams of chlorid (as NaCl) per day. Even after all edema has disappeared, salt must be returned to the diet with the utmost care and must be eliminated again if there is the least sign of the recurrence of edema.

Concerning the amount of fluid which it is desirable to give, there is less certainty. Usually, if salt is sufficiently restricted, extreme limitation of fluid is less important because the organism retains fluid only with equivalent amounts of salt. Extreme limitation of fluids also causes distress. This is, of course, greatly mitigated if no salt is given, perhaps one of the most important reasons for emphasizing reduction of salt. If the latter is kept sufficiently low, patients do not crave water, and little

difficulty is experienced in preventing them from drinking amounts beyond their excretory capacity. In the edematous stages, however, it is best to set an arbitrary upper limit, which should seldom exceed 2000 c.c. for an adult of average size. When edema is rapidly increasing, this limit may be set even lower. When diuresis has begun, more liberal quantities may be permitted. In acute nephritis, at certain times, the sudden administration of large amounts of water may in itself initiate diuresis, usually of a temporary nature.

In order that fluid restriction may be real and not only apparent, the fluid contents of the food must be taken into consideration. Milk has attained a reputation as an especially valuable food in renal disease. In point of actual fact its salt and water content are so great in proportion to its food value that it should be used very sparingly in edematous cases.

Diuretic Drugs.—*Digitalis* cannot be expected to act as a diuretic in true renal edema because the latter is not due to cardiac insufficiency. Nevertheless it is not well to harbor inhibitory preconceptions nor to flatter oneself on diagnostic infallibility. Full justice has not been done the patient with stubborn edema if the effect of a course of digitalis is not sometime tried. Occasionally an unexpected response will be secured, especially in patients with some degree of hypertension, presumably because unrecognized heart failure played a part in the production of the edema.

The *purine diuretics,* caffein, theobromin, theophyllin and their derivatives, are almost invariably ineffectual (Christian and collaborators). The best of them, theocin and euphyllin, not only fail to produce diuresis, but are too likely to cause vomiting and other disagreeable and possibly injurious untoward effects.

Mercurial diuretics, of which novasurol (merbaphen) is at present, the most popular, are highly recommended by Keith and others. Kulcke, Marvin and other observers have reported serious toxic results from their use in renal conditions and advise their restriction to the treatment of non-renal edemas. The author, also, has seen such grave and even fatal poisoning from novasurol that he hesitates to use it in the presence of known renal damage. If it is not successful in producing diuresis it almost invariably causes mercurial nephrosis and even a diuretic effect does not preclude renal injury from its use.

Acidifying Diuretics.—These are salts, the basic ions of which are excreted by the gut or some extrarenal channel or converted into an organic compound, leaving the acid ion alone to act in the body to produce an acidosis (Gamble and collaborators). The two salts generally employed for this purpose are calcium chlorid and ammonium chlorid. Magnesium salts would work equally well if they were not either too toxic or too cathartic. Ammonium chlorid is usually preferred to the calcium salt because it is less disagreeable to take. The ammonia is converted in the body to urea,

leaving the chloridion to produce an acidosis. The administration of ammonium chlorid is, from the standpoint of the internal economy of the body, equivalent to giving hydrochloric acid, but has no direct acidifying effect in the stomach. All internal acidifying measures tend to promote water loss both by way of the kidneys and by other channels, especially the lungs. They are extremely useful diuretics in edema of renal origin.

The dose of ammonium chlorid necessary to cause acidosis in normal individuals is about 20 grams daily. In nephritis somewhat smaller doses, 10 to 15 grams, produce the same effect. It is best administered in a 2 per cent solution or in tablet form. Stronger solutions are likely to cause heart-burn, nausea and vomiting. The fluid with which the drug is given must be taken into account in prescribing. If the tendency to edema is not too great, profuse diuresis may develop and can be maintained for several days, sometimes until the edema is entirely eliminated. If diuresis does not occur, severe acidosis results. This does not evidence itself by the usual symptoms. There is seldom obvious dyspnea or even hyperpnea. The chief symptoms are anorexia, heart-burn, nausea and vomiting. If, when these appear, the drug is not discontinued or its dosage diminished, the blood carbon dioxid may be reduced to a serious extent. In one of the author's cases serum CO_2 fell to 10.3 volumes per cent.

Ammonium chlorid may fail in a given instance to produce diuresis and still prove highly effective in the same case at another time. There are stages in the edematous nephritides when all efforts to induce diuresis prove ineffectual, and when only supportive measures aimed to improve the general condition and state of nutrition of the patient can be employed. When the latter improve, measures that previously failed may, if repeated, be successful. This resistance to diuretics seems to mark either an exacerbation of the nephritis or a period in which the serum proteins are extremely reduced. Gamble has suggested that patients with preëxisting hyperchloremia are more prone to respond to ammonium chlorid than those with normal or low serum chlorids. In the author's experience, no such rule can be established. It is only possible to say that when patients appear generally ill with fever and digestive disturbances and when the serum proteins are extremely low (less than 4 per cent), all diuretics, including the acidifying salts, are likely to be ineffective.

Hyperchloremia is not in itself a contra-indication to the use of ammonium chlorid. In the presence of preëxisting acidosis (reduction of serum bicarbonate) and nitrogen retention it should be employed with great caution.

Keith recommends the use of ammonium chlorid and novasurol in combination. Although the combination may induce diuresis with greater regularity than novasurol alone, it does not insure against mercury poisoning in the exceptional case.

Alkaline Diuretics.—Alkaline salts, which were formerly extensively administered, have now been largely abandoned. Blum and others have demonstrated that alkaline sodium salts, such as the bicarbonate, usually only aggravate edema. Potassium salts are less likely to promote fluid retention and may even induce diuresis, but are far less effective for this purpose than the acidifying salts. Evidently, there is less tendency to retention of potassium than to retention of sodium, an indication, perhaps, that edema affects cells less than it does interstitial fluids.

Urea.—So far has the pendulum swung away from the old tradition that protein and its catabolic products must be eschewed in all types of nephritis, that urea has been recommended and extensively used in large doses as a diuretic in renal and cardiac edema. It was first proposed for this purpose by Wordley and H. McLean who believed that the beneficial effects of high protein diets lay in the diuretic effect of the nitrogenous waste products derived from them, especially urea. This substance may be looked upon as a natural regulator of renal function. It is non-irritating to the normal kidney and has no apparent toxic effects. If large amounts find access to the blood stream from either endogenous or exogenous sources, they can escape only through the kidney and tend to withdraw with them water, if any is available.

Urea is best given in ice cold 20 per cent solution which may be flavored, if desired, with the juice of citrus fruits. The daily dose varies from 20 to 80 grams of the pure drug. The fluid given with the drug must be subtracted from the daily ration if any result is to be expected. The purpose of the urea is to strain the concentrating powers of the kidneys so that they may be forced to draw on the water stores of the body, to enable them to excrete the urea. If extraneous water is provided this purpose is defeated. Slight or moderate grades of nitrogen retention (blood non-protein nitrogen less than 50 milligrams) need not be considered contra-indications to the use of the drug in moderate doses. It is intended to produce just such increases of blood non-protein nitrogen. If there is more serious nitrogen retention the administration of urea, if not contra-indicated, is superfluous; the kidneys are already working under urea stimulation. It is well to determine the fasting blood non-protein nitrogen at intervals during urea treatment. This should not be greatly elevated. If it is high (non-protein nitrogen over 60 milligrams) or shows a tendency to mount steadily, the patient is unable to eliminate the extra urea daily. The blood urea will and must mount to considerable heights in the course of the day, but should fall to a moderate constant level before the following day's dose.

Urea is far more useful for the maintenance of the edema free state in patients with residual hydropigenous tendencies than it is for the production of diuresis. It may be used continuously over long periods without causing any apparent deleterious effects.

Thyroid Extract and Thyroxin.—Eppinger, in 1917, was the first to recommend the use of extracts of the thyroid gland for the treatment of edemas. Epstein, who also advocates their use in the nephroses, has pointed out that the basal metabolism in these cases is usually low and resistant to the action of thyroid. From these facts he argues that the disease is characterized by thyroid deficiency. The argument seems unconvincing, as do the favorable effects from the treatment which have been reported. If these subjects are suffering from malnutrition, this alone can explain the reduction of basal metabolism. Attempts to accelerate it could serve only to aggravate the underlying condition, regardless of their effects on the edema. In the author's experience patients with renal edema have proved to be neither insensitive to nor benefited by thyroid therapy.

Parathyroid Extract.—In the edematous nephritides serum calcium is low. Serum calcium, in other conditions, rises under the influence of extracts of the parathyroid gland. The latter have, therefore, been employed by several workers, especially McCann, in the treatment of renal edema, with alleged favorable results. It is reasonably certain that hypocalcemia in nephritis is not due to parathyroid deficiency, but is a secondary effect of low serum proteins or high serum phosphorus or both. In McCann's cases serum calcium was not seriously influenced by the rather small and infrequent doses of parathyroid extract given, although the diuretic effects ascribed to these were quite prolonged. There are no cogent theoretical reasons for expecting diuresis from parathyroid extract, especially in such small doses. The author has tried both small and large doses in three cases without effect. The results obtained by McCann may have been coincidental with, and not due to, the administration of parathyroid extract. More extensive studies must be presented before its diuretic action is established. McCann gave single doses of 20 to 40 units to adults.

Measures Directed toward the Treatment of Circulatory Disturbances

The circulatory disturbances encountered in nephritis are for the most part secondary to hypertension with or without arteriosclerosis. The treatment of *frank heart failure* has already been touched upon above. It differs but little from that of cardiac decompensation from any other cause, with chief dependence on digitalis. Patients with advanced renal insufficiency are often unusually susceptible to the effects of this drug and exhibit toxic symptoms after relatively small doses, perhaps because they excrete it with unusual difficulty. Except in case of emergency, therefore, it is unwise to give more than $\frac{1}{3}$ or $\frac{1}{2}$ the Eggleston dose in the first twenty-four hours, followed by smaller doses until digitalization is completed. The effect most desired is diuresis and when this is instituted, maintenance

doses only need be given. For this purpose, also, less than the usual quantity often suffices. Vomiting, in the presence of renal insufficiency, is such a serious symptom that there is especial need for avoiding digitalis intoxication. On the other hand, if the patient with heart failure is already vomiting, subcutaneous digitalis, by improving the circulation may check the emesis.

For *the specific treatment of hypertension* many measures have been advocated; but none have proved generally acceptable. Of the drugs advocated the nitrites appear to give slight symptomatic relief of headache and other subjective ailments in a very limited number of cases, but are regularly successful only in allaying anginal attacks. Potassium iodid is falling into disuse as a general placebo now that its true usefulness in thyroid conditions is appreciated. Sulphocyanates have recently been hopefully heralded (Gager). More careful analyses are required, however, to prove that they exert a beneficial effect. The doses recommended by Gager are: for the first week 0.1 gram (1.5 grains) three times a day; for the second week 0.1 gram twice a day and, after that, the same dose once daily.

Allen and Sherrill claim that prolonged use of salt-poor diets causes improvement of hypertension. These claims have not been supported by other observers. Arguments against the use of such diets, in the presence of renal insufficiency, have been advanced above. Before hyposthenuria develops, there are no very good theoretical considerations to guide dietetic control. Some patients experience subjective improvement when they receive large amounts of fluid without salt restriction; others may be benefited by the Allen treatment.

Physical rest is important, especially when there are definite organic vascular changes; but must not be carried to the point where the life that is saved is no longer worth living. Quite as important as physical rest is mental peace. There is an ever-increasing appreciation of the fact that hypertension at its onset is largely due to functional vasomotor disturbances often greatly influenced by, if not born of, psychogenetic factors. Here modern psychiatry may prove a great aid.

Convulsive seizures occurring in the course of nephritis have been looked on in the past as symptoms of uremia. They are now generally believed to be caused by circulatory disturbances and are often spoken of as pseudo-uremic or eclamptic. They are ascribed by Volhard and others to temporary edema of the brain. Whether or not this is the true explanation of any or all such seizures, they may occur in conditions of extreme dehydration as well as in acute nephritis with edema. They are encountered in essential hypertension often before there are demonstrable evidences of renal insufficiency. Blood-letting has long been the standard form of treatment and often appears to be effective. If it is practiced at all, it should be

reserved for patients without anemia. Lumbar puncture sometimes checks convulsions. Blackfan has used intravenous injections of 1 per cent magnesium sulphate with success in children with acute nephritis with hypertension. In adults with eclamptic convulsions we have found it equally useful. It both stops the convulsions and temporarily lowers the blood-pressure. From 500 to 900 c.c. of the 1 per cent solution have been given to normal adults without untoward effects. The injection should be made slowly and should be discontinued as soon as the blood-pressure indubitably falls. The drug probably acts as a sedative. Presumably equally favorable results could be secured by smaller quantities of more concentrated solutions. Such amounts can only be given intravenously; subcutaneously, or intramuscularly, they are quite painful; by mouth they are extremely cathartic. Smaller doses may be given subcutaneously or intramuscularly at frequent intervals for their sedative effects. For this purpose, ampuls containing 50 per cent magnesium sulphate with small amounts of novo-cain, can be obtained on the market.

Occasionally in hypertensive cases, even before marked renal insufficiency has developed, attacks of vomiting are observed. These may lead to tetany. In this case the rational treatment consists in the parenteral administration of normal salt solution.

Dyspnea may arise from two chief causes: cardiac failure and acidosis. These must be carefully distinguished. The dyspnea of heart failure, of course, responds to the usual cardiac treatment.

The acidosis of chronic nephritis is a product of several factors; total salt deficiency is probably the most important of these, while accumulations of foreign acids play a less significant rôle. The patient should be given enough carbohydrate to prevent starvation acidosis and enough sodium chlorid to overcome the salt deficiency. Bicarbonate is less essential in most instances and large doses are seldom required and may cause alkalosis with tetany. There is clear indication for the administration of bicarbonate only when the serum CO_2 remains low after the patient has received enough carbohydrate to prevent ketosis and enough sodium chlorid to bring the serum chlorid to the normal concentration. Only sufficient need be given to allay dyspnea and hyperpnea and to keep them in abeyance. Usually 5 grams daily is quite adequate.

For paroxysmal attacks of dyspnea that sometimes occur in hypertension with or without nephritis, morphin is probably the most generally useful drug. If, as often happens, signs of bronchial spasm (musical rales and squeaks, and expiratory dyspnea) occur, nothing is so effective as small doses of adrenalin given subcutaneously. The extreme hypertension that accompanies these paroxysms is no contra-indication to the use of the drug. If the latter relieves the dyspnea, the blood-pressure usually falls. If the use of adrenalin is restricted to the type of dyspnea described, it is far more effective than atropin which is more commonly used. Vene-

section may be used for the acute pulmonary edema of heart failure, if the patient has not a severe anemia.

Measures Directed toward the Relief of Other Secondary Symptoms Such as Anemia

The pathogenesis of the anemias of nephritis is quite obscure. Hydremia is, the most, a minor contributory factor in a few cases (Brown and Rowntree). No evidence of excessive blood-destruction can be found (Brown and Roth). The blood-picture is apparently uninfluenced by liver and responds but little to iron medication. Temporary improvement may follow transfusions of whole blood. Improvement of the general condition of the patient is usually reflected in a rising blood-count. Although little benefit is derived from treatment directed specifically against the anemia, care should be taken that this is not aggravated by the diets prescribed. Diets consisting largely of milk and starchy foods will cause anemia even in normal animals. Generous quantities of fruits and green vegetables, and judicious amounts of the dreaded "red" meats may do something to prevent the rapid progress of the anemia.

PREPARATION OF NEPHRITIC DIETS

For the exact calculation of diets the reader is referred to standard dietary manuals (see References: Atwater and Bryant, and Report of the Connecticut Agricultural Experiment Station). For the treatment of most cases, especially when they are ambulatory, such exact calculations are not necessary. For these purposes the following system, which is similar in general principles to those proposed by O'Hare and Koehne, is useful.

In Tables I to VI common foods are classified in groups according to the approximate quantities of protein and calories which they contain, and the portions of these foods which offer approximately equal amounts of these components, are indicated. By the proper selection of foods from these lists it is easily possible to make up a diet of any desired composition. By substitutions variety can be secured.

TABLE I—Portions of Food which Contribute 100 Calories without Protein

Sugar	2½	tablespoonfuls
Maple sugar	2½	tablespoonfuls
Marmalade	2½	tablespoonfuls
Jellies	2½	tablespoonfuls
Honey	2½	tablespoonfuls
Butter	1	tablespoonful
Oil	1	tablespoonful
Heavy cream	2½	tablespoonfuls (40 per cent fat)
Mayonnaise	1	tablespoonful
Grape juice	½	glass

Tables VII, VIII and IX serve as examples of the use of the tables. VII is a low protein, low calory diet; VIII a low protein diet with moderately high calories; IX a rather high protein diet with moderate calories. These diets are made up from standard portions taken from the diet lists. The list and the number of standard portions are indicated in columns 3 and 4. All portions given in Tables I to IX are for cooked or prepared foods.

TABLE II—PORTIONS OF FOOD WHICH CONTAIN ABOUT 1 GRAM OF PROTEIN AND
50 CALORIES

Orange ....1 small
Orange juice ....5 tablespoonfuls
Grape fruit ....one half
Apple ....1 average size
Peach ....1 average size
Pear ....1 average size
Banana ....1 average size
Grapes ....1 small bunch
Strawberries ....1 cup
Raspberries ....1 cup
Prunes 2
String beans ....4 tablespoonfuls

TABLE III—PORTIONS OF FOOD WHICH CONTAIN ABOUT 2 GRAMS PROTEIN AND
40 CALORIES

(4 tablespoonfuls of any one of the following)

Beets	Asparagus
Carrots	Lettuce *
Turnips	Onions
Peas	Summer squash
Winter squash	Cauliflower
Brussels sprouts	Tomatoes
Celery	

* The food value of an ordinary portion of lettuce may be neglected.

TABLE IV—PORTIONS OF FOOD WHICH CONTAIN ABOUT 3 GRAMS PROTEIN AND
90 CALORIES

White bread 1   average slice
Graham bread 1   average slice
Shredded wheat biscuit.....1
Oatmeal .... ¼ cup, cooked
Farina .... ½ cup, cooked
Ralston's .... ½ cup, cooked
Corn meal .... ½ cup, cooked
Macaroni .... ½ cup, cooked
Potato 1   small
Potato, mashed .... ½ cup
Potato, baked 1   average slice
Rice .... ¾ cup
Canned corn .... ½ cup
Lima beans .... ¾ cup

TABLE V—PORTIONS OF FOOD WHICH CONTAIN ABOUT 6 GRAMS PROTEIN AND 140 CALORIES

```
Milk ..................... 1    glass
Lamb chop .............. 1    small
Roast lamb .............. ¾ oz. (1 slice, 2½" x 3" x ¼")
Tenderloin .............. ¾ oz. (1 slice, 4" x 1" x ½")
Roast beef ............... ¾ oz. (1 slice, 2½" x 3" x ¼")
```

TABLE VI—PORTIONS OF FOOD WHICH CONTAIN ABOUT 6 GRAMS PROTEIN AND 60 CALORIES

```
Fish .................... 1    oz. (1 slice, 1" x 2¼" x 1")
Oysters ................. 6    medium size
Shrimps ................. 5
Lobster meat ............ ¼  cup
Chicken ................. 1    oz. (1 slice, 3" x 3" x ⅛")
Egg ..................... 1
```

TABLE VII—DIET CONTAINING 50 GRAMS PROTEIN AND 1500 CALORIES

Food	Quantity	Table	Portion	Weight, Grams	Protein, Grams	Calories
Breakfast						
Orange	1 small	II	1	100	1	50
Farina	½ cup	IV	1	30	3	90
Milk	½ glass	V	½	100	3	70
Toast	1 slice	IV	1	30	3	90
Butter	1 tbsp.	I	1	10	0	100
Egg	1	VI	1	50	6	60
Cream	2½ tbsp.	I	1	20	0	100
Sugar	1 tbsp.	I	⅔	10	0	40
Dinner						
Meat	2 ozs.	V	2½	60	12	280
Potato	1 small	IV	1	100	3	90
Beets	4 tbsp.	III	1	100	2	40
Lettuce			1			
Tomato	1 small	III	1	100	2	40
Custard: egg..	½ egg	VI	½	20	3	30
milk..	½ cup	V	½	100	3	70
sugar.	1½ tsp.	I	⅙	5	0	20
Butter	1 tbsp.	I	1	10	0	100
Supper						
Baked potato.	1 small	IV	1	100	3	90
Butter	½ tbsp.	I	½			50
Peas	4 tbsp.	III	1	100	2	40
Peaches	1 small	II	1	100	1	50
Egg	1	VI	1	50	6	60
Cream	2½ tbsp.	I	1	30	0	100
Sugar	1½ tsp.	I	⅙	5	0	20

TABLE VIII—DIET CONTAINING 60 GRAMS PROTEIN AND 3000 CALORIES

Food	Quantity	Table	Portion	Weight, Grams	Protein, Grams	Calories
Breakfast						
Orange	1 small	II	1	100	1	50
Farina	½ cup	IV	1	30	3	90
Milk	½ glass	V	½	100	3	70
Toast	1 slice	IV	1	30	3	90
Egg	1	VI	1	50	6	60
Butter	1 tbsp.	I	1	10		100
Sugar	1 tbsp.	I	⅔	10		40
Cream	2½ tbsp.	I	1	30		100
Marmalade ...	2½ tbsp.	I	1	30		100
Dinner						
Meat	2½ oz.	V	3	70	15	350
Potato	1 small	IV	1	100	3	90
Beets	4 tbsp.	III	1	100	2	40
Lettuce			1			
Tomato	1 small	III	1	100	2	40
Mayonnaise ..	2 tbsp.	I	2	20		200
Custard: egg..	½	VI	½	20	3	30
milk..	½ cup	V	½	100	3	70
sugar.	1½ tsp.	I	⅙	5		20
Sugar for tea.	1 tbsp.	I	⅔	10		40
Butter for meal	2 tbsp.	I	2	20		200
Supper						
Baked potato.	1 small	IV	1	100	3	90
Butter	2 tbsp.	I	2	20		200
Carrots	4 tbsp.	III	1	100	2	40
Peach	1 average	II	1	100	1	50
Cream	5 tbsp.	I	2	60		200
Bread	1 slice	IV	1	30	3	90
Meat	2 oz.	V	3	60	12	280
Sugar	1 tbsp.	I	⅔	10		40
Grape juice...	1 glass	I	1	200		200

The average adult takes from 10 to 15 grams of chlorid (as sodium chlorid) daily in his diet. Limitation of salt involves something more than the injunctions to add no salt to the food at table and to avoid obviously salty foods. Salt must not be used in the preparation of foods. The use of most tinned and ready-prepared foods must be avoided because salt has been added in the process of manufacture. Bakers' bread cannot be used if strict limitation is desired and should never be given in unrestricted quantities. Salt butter must not be used. Milk contains almost 1 per cent of NaCl and must be used sparingly in consequence. If care is taken to regard these simple rules it is not difficult to restrict the salt intake of even a generous diet to 1 to 3 grams of sodium chlorid daily. Stricter limitation is seldom necessary and hardly consistent with palatability. It has been recommended, however, by Allen and Sherrill and

TABLE IX—DIET CONTAINING 100 GRAMS PROTEIN AND 2500 CALORIES

Food	Quantity	Table	Portion	Weight, Grams	Protein, Grams	Calories
Breakfast						
Orange	1 small	I	1	100	1	50
Farina	½ cup	IV	1	30	3	90
Milk	1 glass	V	1	200	6	140
Toast	1 slice	IV	1	30	3	90
Butter	1 tbsp.	I	1	10		100
Eggs	2	VI	2	100	12	120
Sugar	1 tbsp.	I	⅔	10		40
Cream	2½ tbsp.	I	1	30	.	100
Dinner						
Meat	4 oz.	V	5	120	24	560
Potato	1 small	IV	1	100	3	90
Beets	4 tbsp.	III	1	100	2	40
Lettuce			1			
Tomato	1 small	III	1	100	2	40
Mayonnaise ..	½ tbsp.	I	½	5		50
Milk	1 glass	V	1	200	6	140
Butter	1 tbsp.	I	1	10		100
Custard: egg..	½	VI	½	20	3	30
milk..	½ cup	V	½	100	3	70
sugar.	1½ tsp.	I	⅙	5		20
Supper						
Milk	1 glass	V	1	200	6	140
Baked potato.	1 average	IV	1	100	3	90
Peas	4 tbsp.	III	1	100	2	40
Bread	1 slice	IV	1	30	3	90
Cream	5 tbsp.	I	2	60		200
Meat	3 oz.	V	4	90	18	420
Butter	1 tbsp.	I	1	10		100

others and means for insuring such limitation are described by these authors.

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CHAPTER LIV

THE PLACE OF MALARIA IN THE TREATMENT OF
GENERAL PARALYSIS (PARESIS)

Henry Alden Bunker, Jr.

The treatment of general paralysis by "non-specific" measures, as by inoculation of the patient with tertian malaria, may fairly be said to have now passed beyond the experimental stage; and having done so, it takes rank among the most brilliant therapeutic discoveries of the present century, in recognition of which Wagner-Jauregg has recently received the Nobel prize. The very considerable number of patients thus far treated, the notable proportion of these in whom a definitely favorable therapeutic result has been achieved, and the now rather significant subsequent length of time over which many of them have been observed, have combined to convince the majority of those who have employed it that the malaria treatment, in its demonstrated influence upon a disease formerly intractable to every means of therapeutic attack, has abolished all present-day justification for the legitimate nihilism of former years as to what it is possible to accomplish in the treatment of general paralysis. Without too dogmatically asserting that the malaria treatment is from every standpoint superior to all other modern methods of therapy, it is certainly not too much to say that its employment in cases of general paralysis holds out a possibility at least as good as, if not indeed actually better than, that offered by any other means at our disposal of (1) arresting the disease in a considerable percentage of cases (as judged, at least, by an apparent non-progression of the disease over protracted periods of time), and of (2) bringing about in consequence, in a certain by no means insignificant proportion of these patients, *especially if treated sufficiently early,* a more or less complete restitution, extended in duration and even perhaps permanent, of mental and physical health. In point of fact it would appear that our present experience with the non-specific treatment of general paralysis has gone far to vindicate Spielmeyer's pronouncement of many years ago that theoretically there is nothing about the pathological process which characterizes this disease that excludes the possibility of therapeutic success. For that possibility has been realized to an extent hitherto unknown.

The malaria treatment of general paralysis owes its origin to the genius of one who was able to appreciate the significance, and make a

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deliberate and rationally planned application, of the centuries-old obser-
vation that certain mental disorders were ameliorated or even apparently
cured through the agency of an intercurrent acute infection; and Wagner-
Jauregg himself observed that various general paralytics who happened to
acquire an intercurrent infectious disease, seemed to do better than those
in whom nothing of this kind occurred. Working from 1887 onwards, first
with tuberculin and subsequently with various vaccines as fever-producing
agents, he came finally to the conclusion that tertian malaria might furnish
the most effective and convenient means of inducing fever of considerable
degree, yet relatively safe in character and readily subject to control. The
validity of this supposition, which Wagner-Jauregg put to the test upon
nine patients in 1917, and upon a larger group in 1919, has since been
amply borne out.

In its general outline the technic of the malaria treatment is simple.
Inoculation is done with from 1 to 5 c.c. of citrated blood (1 part of a
2 per cent solution of sodium citrate to 9 parts of blood) taken directly
from a malarial patient, injected intravenously by preference, since the
incubation period is shorter and of more uniform length when an intra-
venous rather than a subcutaneous inoculation is done. For the obtaining of
malarial blood it is usually necessary to have recourse to a hospital which,
by virtue of a sufficiently large admission rate, is able to carry on the
malarial treatment continuously through being in a position to transmit
malarial blood from donor to recipient in unbroken sequence. It is not
necessary that such a hospital be close at hand, for malarial blood will
remain active, without any precautions being taken as to temperature,
for well over forty-eight hours, particularly if a few drops of a 50 per cent
solution of glucose are added to it. Five to seven days after the intravenous
injection of the blood, but sometimes earlier and occasionally later, there
occurs a rise of temperature which usually lasts one to three days; the
fever may be continuous but is frequently remittent, each remission tend-
ing to be followed by a rise of temperature higher than the level previously
reached, so that the chart of this so-called "initial fever" may resemble
that of the first week of typhoid fever. This phase is rather variable both
as to duration and degree of fever, but usually after two or three days of
gradually rising temperature the patient embarks without further prelude
upon the first malarial rigor, which, as is well known, is characterized by
a more or less abrupt rise of temperature to 103° to 105° F., usually
accompanied by a severe chill of some twenty to forty minutes' duration
occurring at the very onset of the rise of temperature. The fall of tempera-
ture, accompanied by profuse sweating, is much more gradual, so that
the entire duration of the febrile attack, from normal temperature to
normal temperature, is often as much as twelve or fourteen hours. Thence
forward the malarial paroxysms occur at daily intervals in rather the
majority of cases; a true tertian course appears to be somewhat the excep-

tion in inoculation-malaria. Because the daily occurrence of the rigors is undoubtedly a greater tax upon the patient than less frequent febrile attacks would be, methods of giving small doses of quinin have been devised for the greater spacing out of the malarial paroxysms, but here we cannot enter into a description of these measures, which are still somewhat in the experimental stage and find their greatest sphere of usefulness in elderly or debilitated patients or those who seem on one ground or another to constitute poor risks. Though we have no real criterion of how much malaria is "enough" in the given case, in the majority of patients it appears to be amply sufficient to allow eight to twelve febrile paroxysms, the temperature rising in nearly all of them to a maximum of at least 103°-104° F., and often to 105° or even 106° F. When it is desired to terminate the course of fever, quinin is given at the rate of 10 grains three times a day; one further febrile attack often occurs subsequent to the first full day of quinin administration, but this additional paroxysm can frequently be prevented by an initial large dose of quinin (20 to 30 grains). Continuation of quinin for a week is ample for the destruction of all malarial parasites. No other medication is employed, save that it is now almost everywhere customary to give caffein as a routine, 3 grains three times a day, throughout the febrile period. Mild gastro-intestinal symptoms, herpes, mild jaundice, and edema of the ankles are more or less frequent complications which may usually be disregarded. In the opinion of some, a definite rise in the blood-urea or especially a fall of the systolic blood-pressure to 90 millimeters, is an indication for terminating the infection, as is also severe toxemia or exhaustion, intractable diarrhea, or persistent vomiting. In general, patients under forty years of age, seldom, in our experience, develop alarming symptoms of any kind, and accidents are rare; it is the markedly debilitated, the elderly (over fifty-five or sixty), and the very obese in whom infection with malaria entails a more or less considerable risk, with an unfavorable outcome in a certain proportion. But it has been demonstrated that the mortality in which the malaria itself plays a part, can be kept as low as 5 per cent—a figure which assuredly compares favorably with the eventual 100 per cent mortality of untreated general paralysis. It must be added that the recent improvements referred to above, in conducting the course of the malarial infection, have reduced the number of conditions formerly considered as contra-indications to treatment with malaria; and some clinics now treat all patients practically without selection.

It is an undoubted fact that patients differ very considerably in their susceptibility to malarial infection. In a rather appreciable proportion the infection appears to die out spontaneously after two to seven or eight febrile attacks have occurred, although not infrequently it may then be reactivated by reinoculation with malaria or by a "provocative" intravenous injection of typhoid vaccine or other foreign protein, provided that

plasmodia are still demonstrable in the blood. In still a few other patients the original inoculation is entirely without result; in some of these a second or even a third inoculation may be partially or altogether successful; a very small minority it seems impossible to infect with malaria at all, this being particularly the case among negroes. When it appears impossible to get the infection successfully established or reëstablished, recourse has to be had to some other fever-producing agency, such as relapsing fever, sodoku, or injections of typhoid vaccine.

One of the most immediate results of the malaria treatment, appreciable within three to six weeks of its termination, is the very marked sense of well-being not infrequently expressed by the patient; rather commonly he asserts that he has not felt so well for years. Within the same period there begins the gain in weight which characterizes the majority of malaria-treated patients, and which not only counterbalances the weight loss of the febrile period (often amounting to 10 to 15 pounds), but frequently very materially exceeds it. Improvement in the mental symptomatology has its onset anywhere from actually during the course of the fever to six or eight weeks after its conclusion; it is usually of very gradual evolution, and reaches nearly its maximum for the given case two months to six months subsequent to the termination of the malaria. As a working rule, it may be said that any mental improvement which has not taken place at the end of six months will not occur at all; but this holds true chiefly of the grosser symptoms, and in not a few patients improvement of a subtle order continues to go on very definitely for a period of six months or a year or longer.

Far more gradual in its evolution is the modification in the spinal fluid pathology which the malaria treatment eventually brings about in a very appreciable proportion of cases; one to two years, for example, is often required for definite modification in the strength of the Wassermann reaction in the spinal fluid to come about, although reduction of the cell-count to normal is almost always more or less immediate. In a certain proportion, perhaps one-quarter or more of all cases, indeed, *the Wassermann reaction in the spinal fluid ultimately becomes completely negative,* without the use of any supplementary form of antisyphilitic treatment. This is extremely worthy of note; for when it is considered that general paralysis is, as regards the spinal fluid, the Wassermann-fast condition *par excellence,* that a large number of intraspinal injections of arsphenaminized serum, or upwards of 100 or 150 injections of tryparsamid, are required to produce Wassermann-negativity in the few cases in which such a mode of treatment is able to produce this result at all, it is obvious that we have here one of the most striking and fundamental effects, though not the most dramatic, which the malaria treatment is capable of bringing about.

What have been, in terms of actual figures, the clinical results obtained

by various observers, which have been such as to lead the great majority
of them to agree that malaria treatment is the treatment of election in
general paralysis because its effectiveness in combating that disease is
scarcely equaled and certainly not surpassed by any other mode of therapy
at our command? An answer to this question is conveniently at hand in
the compilation recently published by Driver and his associates of all the
malaria-treated cases of general paralysis recorded in the literature to
April 1, 1926. From this tabulation, slightly modified from the original
by the inclusion of 165 patients treated by the writer from June 1, 1923,
to March 1, 1928, it appears that out of a grand total of 2,460 patients,
no less than 27.5 per cent achieved a complete remission of mental symp-
toms, with residual mental defect absent or minimal, and with a more or
less completely regained capacity to resume their previous occupations;
while an additional 26 per cent attained an incomplete remission, with
an apparent arrest of the disease, but with a persistence of residual defect
symptoms sufficient to preclude a resumption of the former vocation yet
not necessarily enforcing continued hospitalization or rendering impossible
the following of some gainful occupation.

SYNOPSIS OF MALARIA-TREATED CASES OF GENERAL PARALYSIS RECORDED IN THE
LITERATURE TO APRIL 1, 1926 (DRIVER, GAMMEL AND KARNOSH)

Cases	Number	Per Cent
Greatly improved (full remissions)	676	27.5
Moderately improved (incomplete remissions)....	630	25.6
Unimproved (condition worse, or died)...........	1,154	46.9
TOTAL	2,460	100.0
Definitely affected by treatment.........		53.1
Little or not at all affected		46.9

It should not fail to be observed that *53 per cent of all these patients
were affected in a definitely favorable sense by the malaria treatment,*
while 47 per cent were little or not at all affected by it or were influenced
in only a very temporary manner. Since in certainly the majority of these
2,460 patients commitment to an institution had been necessitated before
treatment was begun, it is quite reasonable to suppose that, had treatment
been undertaken earlier in the course of the disease, a certain and perhaps
considerable number of those who achieved a moderate improvemnt would
have fallen within the more fortunate group of the greatly improved. For
it is unquestionable that this more favorable outcome would have charac-
terized many at least of the only moderately improved, had not degenera-
tive changes beyond the possibility of restitution of function already oc-
curred when treatment was commenced, so that in these patients a maximal
therapeutic result was precluded by an adventitious factor having no real

bearing upon the efficaciousness of the malarial treatment itself.[1] In many, even if not perhaps in all of these patients whose benefit was submaximal, the malaria treatment was fully as effective against the disease itself as in their more fortunate fellows, but the practical result obtained in these patients was imperfect because malaria could not undo structural damage which had already been done. It is on this account that we hold that the total proportion of patients affected in a definitely favorable sense by treatment (53 per cent) is the truer measure of the actual possibilities of the malaria treatment in dealing with general paralysis, and it is on this same account that we shall later emphasize the importance of early recognition of the disease.

Having established what the immediate therapeutic results are which the malaria treatment is capable of bringing about in largely unselected cases of general paralysis (and furthermore what results might legitimately be expected were many of these patients to receive malaria treatment prior to the outbreak of a frank psychosis), the question of greatest practical interest becomes: What of the duration of these favorable results—how long do they last? Are the remissions ever permanent, and can we speak of a "cure"? Do they persist longer than is in general true of the spontaneous remissions which occur in some 4 to 6 per cent of untreated general paralytics? To these questions we can give at least provisional answers. It should be stated at the outset that where definite clinical improvement occurs at all, it may be of the most variable duration; it may last only a few weeks, for example, or even only a few days, and yet be rather well marked, though so soon followed by relapse and retrogression. Speaking generally, however, it is safe to say that, on the whole, the better the therapeutic result obtained, the more likely it is to be of a more or less enduring character.

For the sake of brevity let us confine our consideration to the present status of certain paretic patients who evidenced a complete remission of their disease in consequence of malaria treatment given them five to ten years ago. (1) Of the small group treated by Wagner-Jauregg, in 1917, five attained complete remissions; of these five, three are still alive and

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[1] A possibly valid corroboration of this point of view is found in our experience with the response to malaria treatment of female patients as compared with male. Complete remissions were observed in 32 per cent of 165 male patients but in only 12 per cent of 67 females—an experience similar to that of other workers; but of incomplete remissions there were 11 per cent among the males and over 19 per cent among the females. Thus, if complete and incomplete remissions are considered as a single group, the discrepancy is less pronounced: 43 per cent of the males *versus* 31 per cent of the females. We have interpreted this diminished proportion of complete remissions and increased proportion of incomplete remissions among the female patients as being possibly due to the fact that the economic situation of most women of the hospital class makes it less imperative that cognizance be taken by their immediate family of a reduction in efficiency and a general mental deterioration on their part, so that they are brought to the hospital for treatment at a later stage, on the average, than is the wage-earning male.

in an unchanged state of complete remission at the end of nine and one-half to ten and one-half years. (2) Of the twenty-five patients treated by Gerstmann in the latter part of 1919 and the early part of 1920, nine eventually attained a complete remission and four an incomplete remission; eight of the former and three of the latter have maintained that status throughout a period of very nearly eight years. (3) Of fourteen complete remissions obtained at the New York State Psychiatric Institute between June 1, 1923, and June 1, 1924, twelve have preserved that state to the full throughout a period of five to six years. In sum, though it may be still too soon to speak of these patients as definitely and permanently "cured," we find that *out of twenty-eight patients who originally attained a complete remission, twenty-three are still in that state at the end of five to ten years.*

As we have said, the therapeutic results thus far reported have been obtained for the greater part in patients whose disease was sufficiently advanced and whose mental symptoms were in consequence sufficiently outspoken so that commitment to a mental hospital had already been necessitated before treatment was instituted; so that it is entirely conceivable, as we have intimated, that earlier treatment would have led to even more satisfactory results. Thus, the importance of early diagnosis is manifest. Indeed, the very fact of now possessing a really effective method of attack makes early diagnosis of the utmost importance, since something —in fact a great deal—can now be done about it. The situation is, therefore, very different from that of a decade ago, when general paralysis was a disease of such entirely hopeless prognosis that failure to recognize it promptly was in no way prejudicial to the patient. There is, in fact, some analogy herein to the introduction of diphtheria antitoxin, which caused the prompt recognition of diphtheria to become a far more vital matter than it had previously been. But general paralysis is, in the majority of instances, a disease of extremely insidious onset, and its early recognition correspondingly difficult—or rather, the procedures which would usually lead to a definite diagnosis, are frequently not readily suggested by the symptomatology; this despite the fact that fully developed cases of the disease, especially when "typical," seldom present serious diagnostic difficulty. In view, then, of the now much increased importance of early diagnosis, a brief review of the question of diagnosis may not be out of place.

A large number, indeed the great majority, of those eventually committed to a mental hospital on account of general paralysis, pass through a prodromal stage of varying character and duration, of which the earliest onset may antedate the appearance of outspoken mental aberration by as much as two years or even longer. This prodromal period, sometimes referred to as the "neurasthenic" stage of the disease, is characterized by the presence of any one or of several of such indefinite complaints as

"nervousness," fatiguability, loss of interest and diminution of initiative, a "run-down" condition, sleeplessness or the reverse, loss of weight in the presence of a normal or even increased food intake, gastric disturbance in the absence of a previous history thereof, vague rheumatoid pains, preoccupation or inattentiveness or "absentmindedness," irritability, and slight changes in character and disposition often consisting only of a mild exaggeration of traits normal to the patient and usually so subtle, especially at first, as to be perceptible only to those most intimately associated with him. Into certain of these symptoms the patient often has insight in that he realizes their presence; of others he is entirely ignorant, and only the members of the immediate family are aware of the subtle and gradual change in one respect or another which has come over him. Needless to say, in not one of these symptoms, not even forgetfulness, is there anything really characteristic of general paralysis as later seen and as commonly thought of, or indeed of neurosyphilis of any type; rather, the patient presents as often as not a clinical picture suggestive of a neurosis, so called. What it is here desired to emphasize is that the presence of one or more of these indefinite, equivocal, and in themselves entirely undistinctive symptoms calls for the adoption of one or both of two procedures: (1) examination of the pupillary reflexes and of the knee-jerks and ankle-jerks; (2) the taking of blood for a Wassermann reaction. The former is a routine procedure which should scarcely occupy three minutes; but whereas the absence of pupillary abnormality or reflex changes does not exclude neurosyphilis, their detection will insure that "nervousness" shall not demand simply a "rest cure" in the face of these physical signs, nor a definite change in the patient's character or disposition be set down exclusively to worry or "nervous strain"—an error surely as great and nowadays as unfortunate for the patient as it would be in the case of early tabes (a disease slightly less common than general paralysis, by the way) to allow lightning pains to pass as "rheumatism" or "neuritis" in the face of absent pupillary light reflexes or knee-jerks, "slow" bladders to be called stricture, or gastric crises to be operated on as gall-bladder attacks (as Stokes has pointedly remarked). When such neurologic signs as these are definitely present, in the interest of the patient an examination of the spinal fluid is assuredly demanded. Similarly, a positive Wassermann reaction in the blood is an indication for lumbar puncture; for, entirely apart from the fact that at least 90 per cent of all general paralytics exhibit a strongly positive Wassermann reaction in the blood-serum, in the presence of syphilis one must determine the presence or absence of neurosyphilis if the interests of the patient are to be safeguarded—and only the more emphatically is this true when the patient manifests such symptoms as have been named above, which, although entirely without diagnostic value in themselves, may take on a significance in the presence of either of the two objective findings just mentioned which they could hardly otherwise

possess. Even, indeed, in the absence of a positive Wassermann reaction in the blood or of suspicious neurologic signs, the occurrence of such symptoms, when they cannot be adequately accounted for on other grounds, should suggest their possible neurosyphilitic etiology as something to be kept in mind, and should raise the question of the desirability of examination of the spinal fluid. For it can safely be laid down as a rule that the presence of any nervous or mental symptom whatever, if that symptom cannot be explained beyond a reasonable doubt on some other basis, is cause for making an examination of the spinal fluid; such is the protean character of neurosyphilis and of its subspecies, general paralysis.

The crucial factor, then, in the diagnosis of neurosyphilis, and *a fortiori* of general paralysis, obviously lies in the examination of the spinal fluid; and the essential practical problem involved consists in the recognition of the indications for such examination. Without the recognition of these indications, examination of the spinal fluid will not be made and the true meaning of such symptoms as have been outlined above, will not be appreciated until frank manifestations of mental disorder eventually supervene and much valuable time has in the meanwhile been lost. But once examination of the spinal fluid is made, the presence or absence of neurosyphilis is established beyond peradventure.

Given a case thus proved to be neurosyphilis, the further question arises whether the patient is an incipient paretic, in which event it would become imperative to adopt forthwith the modern therapeutic measures which alone offer the possibility of prevailing over that form of syphilitic disease of the central nervous system. Without entering into the differential diagnosis here involved further than to remark that the symptoms presented by the patient are more often than not of very doubtful differentiating value, and that the only certainty in this regard is that a weakly positive Wassermann reaction in the spinal fluid (negative with 0.2 c.c., and especially with 0.5 c.c.) speaks unequivocally against the paretic form of neurosyphilis, it is sufficient to say that two possibilities are open: (1) In the absence of reliable evidence to the contrary, to assume in the interest of the patient that he presents a refractory form of neurosyphilis for which the most active type of therapy is definitely demanded—for, after all, the more benign form of neurosyphilis (cerebral syphilis, so called) is no contra-indication to the use of malaria treatment. (2) If for one reason or another it appears desirable to employ malaria treatment only in the event that the presence of paretic neurosyphilis is certain, one may first prescribe a course of twelve injections of arsphenamin or neo-arsphenamin on the basis that a previously strongly positive Wassermann reaction in the spinal fluid will usually undergo some modification if the neurosyphilis is of the non-paretic type, but will remain absolutely unchanged if of the paretic type. The essential point is that the existence of known or probable neurosyphilis of the paretic type, or the presence of any

doubt upon the point, makes the employment of malaria treatment in the highest degree advisable in any such case; and this upon the double ground that, (1) as we have seen, treatment with malaria is of proven efficacy in neurosyphilis, most especially of the paretic type, and in particular the outlook for full recovery of mental health with an absence of residual manifestations of organic damage is especially favorable in early cases of the disease; and (2) treatment with malaria consumes but three weeks, in most instances, from start to finish, so that a decisive blow is, therefore, struck at once and without delay, leaving available an unlimited period during which, without prejudicing the patient's outlook through loss of valuable time, further antisyphilitic treatment of a more protracted and time-consuming character may be given, if so desired.

CHAPTER LV

NON-SPECIFIC PROTEIN THERAPY OF MULTIPLE SCLEROSIS

G. Alexander Young and A. E. Bennett

The incidence of multiple sclerosis makes this disease a therapeutic problem of major importance. In the 1923 edition of Oppenheim's *Lehrbuch der Nervenkrankheiten,* multiple sclerosis is described as the most frequent of all chronic organic diseases of the central nervous system other than neurosyphilis; Marburg makes the same statement; Dana gives its rate of frequency as 0.058 per cent based upon 70,000 neurological cases; Bailey states that of 6916 cases of organic nervous disease and injuries 511 or 7.4 per cent were classed as multiple sclerosis or 0.073 per cent of the 69,394 cases of nervous and mental disease found in the examination of the American draftees and volunteers in the late war.

Notwithstanding the frequency of its occurrence and the amount of clinical study and medical research applied to it, the etiology of this disease remains unknown. Most authorities are of the opinion that the disease is of infectious origin, although Strümpell, Müller, Ziegler, and more recently, Klingman have asserted that endogenous factors, such as a predisposition to neuroglia overgrowth or misplaced embryonic neural elements are responsible for the sclerotic patch formation. The frequent development of the disease following acute infectious diseases, the occurrence of occasional apparently well-authenticated cases attended by a mild febrile reaction, the presence of the characteristic remissions, the finding of periaxal neuritis (Marburg and Hassin) as an early pathologic histological lesion, are factors that weigh strongly in favor of the infectious or toxic causation of multiple sclerosis. Several investigators, Spiller, Byrnes, and others have believed that syphilis in some way influences the development of the disease and have advocated the use of arsphenamin in its treatment.

Much interest has been awakened by the work of Kuhn and Steiner, Marinesco, Kalberlach, Adams, Blacklock and McCluskie, who have found spirochetes in smears taken from the brains of patients and of animals inoculated with the blood and spinal fluid of patients suffering from multiple sclerosis. Teague, in an attempt to corroborate these findings, was unable to substantiate a spirochetal etiology and Collins and Noguchi, in their researches, were likewise unable to agree with this attractive hypothesis.

Because of the general conviction of an infectious origin of multiple sclerosis as voiced by such observers as Oppenheim, Marburg, Spiller, Dana and many others, and encouraged by the striking remissions occurring in paresis after malarial inoculation, various forms of non-specific protein therapy have been tried in the treatment of multiple sclerosis. It has been shown that malarial inoculation is not a specific form of treatment of paresis, as apparently equally good results have been reported with injections of typhoid vaccine, and in the writers' experience, the change from a dysarthric disoriented tremulous paretic to an individual in full remission, capable of resuming work, has been just as striking after typhoid injections as after malarial treatment.

It would seem that the mechanism responsible for the therapeutic effects of non-specific protein therapy such as are observed in typhoid fever, arthritis, diseases of the eye, and various other inflammatory reactions both acute and chronic, local and general, should have an application in the treatment of multiple sclerosis. That such is the case is, we believe, warranted by observations recorded in the literature and by our own experiences. How large the scope of non-specific protein therapy in multiple sclerosis will prove to be, what constitutes the most effective technic and what are the agents most suitable for this particular disease, are problems that await solution through the careful analysis of empirical data provided by extensive experience.

The development of non-specific protein therapy in the neuropsychiatric field had its inception in the work of Wagner-Jauregg, who some thirty-five years ago, noting the remissions following intercurrent acute infectious disease, treated paresis with injections of tuberculin and sodium nucleinate. In 1917 he began the use of malaria vaccine. In other branches of medicine, the same empirical origin of this form of therapy was observed. But scientific study of the subject did not occur until after the introduction of specific vaccine therapy, when it became evident that the therapeutic results were not always caused by specific agents but that the same results could be obtained by agents in which the quality of specificity was not present. Instead of bacterial vaccine, it was found that milk, peptone, albumose, colloidal suspensions of the heavy metals were equally effective.

The literature concerned with non-specific protein therapy has become very extensive. Petersen in his work, *Protein Therapy and Non-specific Resistance,* published in 1922, cites in his bibliography over 1000 articles. Of the outstanding publications the following may be noted. Rumpf, in 1893, published an article on the treatment of typhoid by pyocyaneus vaccine, citing thirty cases with two deaths; in 1911, Renaud reported the treatment of various inflammatory conditions with typhoid vaccine; in 1915, Kraus reported favorable effects in puerperal infection with colon vaccine; in 1916, Schmidt introduced the use of milk as a means of protein therapy, while in this country, in 1912, the much advertised phylacogens

had their temporary popularity. Since 1915, the phenomena of the allergic reaction to parenterally introduced foreign proteins have become known through the work of Vaughn, Opie, Jobling and many others, while in Germany, Weichardt, Mathes and others have published their studies of the biological reactions involved in protein therapy.

These reactions may be summarized under two headings: (1) the general reaction, and (2) the focal reaction.

The general reaction may or may not begin with a chill and fever according to the agent used. In the succeeding twenty-four hours there may be found an increased leukocyte count of 20,000 to 30,000, increased permeability of the tissue-cell walls and of the capillaries with an increased lymph flow, a mobilization and increase of the antibodies and proteolytic and lipolytic ferments in the circulating blood, an increased glandular activity and a heightened nervous irritability. There is also a marked increase of the nitrogen metabolism with a nitrogen excretion in excess of the nitrogen introduced into the system. Mathes asserts that increased protein destruction in the liver is the fundamental phenomenon of the general reaction. Following the first twenty-four hours of the general reaction, a phase of lessened permeability of the capillaries and tissue-cell walls occurs with an apparent desensitization of the tissue cells to circulating toxins. Rusznyak and Koranyi have brought forward evidence showing that in animals sensitized to horse serum an intramuscular injection of milk will so desensitize the animal that no anaphylactic reaction occurs the following day upon the injection of serum. Most investigators have stressed the euphoria that occurs the second day, which has been explained by the destruction of toxic protein split products and by the presence of the desensitization process.

The focal reaction consists of a diphasic primary activation of the morbid processes in the local lesion and a secondary subsequent diminution of the same processes. In a chronic inflammatory locus there would be first congestion with increased exudate from the capillaries and resulting edema and swelling. The inflamed area is flooded with an added amount of enzymes and antibodies, and a corresponding acceleration of proteolytic digestion and of detoxication takes place. This phase is followed by diminished exudate and a reduction of the inflammatory processes of congestion, swelling and pain. The focal reaction comes to an end in from approximately two to four days with an improvement, in properly selected cases, of the focal lesion.

Theoretical explanations of the strikingly favorable effect of non-specific protein therapy in both general and local infections have been numerous. Increased antibody and enzyme mobilization, leukocytosis and accelerated lymph flow have been mentioned by various authors. Probably the most generally accepted hypothesis is that of Weichardt who advances the concept of an omnicellular plasma activation by which he means a

stimulation of all the cells of the organism, resulting either in the production of specific antibacterial agents or in a speeding up of the processes of detoxication by enzymatic lysis or synthesis of the toxic protein split products present in the body. This theory has been amplified by Petersen who adds to Weichardt's explanation by calling attention to the alteration in the permeability of the cellular membrane, which brings about, first, the lymphagogue effect due to the diffusion of plasma with its contained enzymes and antibodies into the lymph spaces, and second, an increased tolerance to intoxication resulting probably from the diminished permeability of the cell wall, which follows the primary increase of permeability. The desensitization of the organism as noted by Rusznyak and Koranyi, may be considered in this connection. In view of the present uncertainty of the actual physicochemical processes that constitute immunity, it is to be expected that the above mentioned hypotheses will require modification.

The field of therapeutic application of protein therapy as judged from a perusal of the literature may be briefly summed as including chronic inflammatory focal lesions and general infections in their early stages. The favorable results of early treatment in the latter and the lack of such good effects in later stages of such general infections have been repeatedly mentioned. Experience alone will show to what extent multiple sclerosis comes within the above category. Whether multiple sclerosis is to be considered as a systemic infection with focal lesions in the nervous system is yet to be determined.

Gross, in 1924, published his results in the treatment of multiple sclerosis by the use of malaria, typhoid vaccine and typhoid vaccine plus neosalvarsan respectively. His conclusions were that typhoid vaccine was more efficacious than malaria; that in the cases treated by typhoid vaccine consisting of all types and stages there were marked remissions in 27.6 per cent and that he believed combined vaccine and neosalvarsan treatment gave best results.

MacBride and Carmichael treated seventy cases at the National Hospital, London, with typhoid vaccine inoculations and silver salvarsan. As a result of their observations they conclude this method of treatment offers more satisfactory results than any other recognized method.

Schackerl reported in 1924 an extensive study in the treatment of multiple sclerosis by the combined use of calcium, neo-arsphenamin and typhoid vaccine injections. He used calcium chlorid because of its antispasmodic effect in hypertonic muscular conditions. His final technic was to dissolve the neo-arsphenamin in 10 per cent calcium chlorid solution, using 10 c.c. He gave two injections a week, one of calcium chlorid combined with typhoid vaccine and arsphenamin and one of calcium chlorid and typhoid vaccine. Although he used the typhoid vaccine for the development of a febrile reaction he did not believe high fevers were essential in the treatment, but that subfebrile or low fever reactions were preferable.

The typhoid vaccine was given first subcutaneously, one c.c. of 250 million bacteria. Then intravenous injections were begun with very small doses, and gradually increased until one c.c. undiluted was given intravenously without reaction. Eighty-seven patients were followed through with this treatment. The author gave the following results in sixty-four cases: forty were very much improved, six of the forty without symptoms, sixteen were improved and eight unchanged. By "very much improved" he meant a disappearance of subjective symptoms but a persistence of slight objective spastic signs such as light clonus, light ataxia, and exhaustible Babinski reflex. In the six cases without symptoms all objective findings were absent except sluggish or absent abdominal reflexes and increased tendon-jerks. In the improved cases subjective symptoms remained but were fewer than at the beginning, while objective spastic signs persisted. On the whole his results were best where the disease had been of short duration. In cases of over five years' standing no complete remission could be produced. A decided improvement was seen in one patient, thirty-nine years of age, with the disease of eight years' duration.

The author concludes that prompt remission can be produced by the therapy in suitable cases with at times astonishing results. He finds that the cranial nerve palsies and cerebellar symptoms quickly disappear but the spastic findings are more difficult to improve. He believes that duration of illness and age influence the results of the treatment unfavorably and that young cerebellar cases appeared to be of the more favorable prognostic type.

Dreyfus and Hanau, in 1926, reported the treatment of ten cases with typhoid vaccine and of twelve cases with malaria. The duration of the disease in the typhoid treated cases was from one to seven years; seven of these patients had been ill for over four years. There were seven progressive cases and three of the remitting type. Of the seven chronic progressive cases only two improved. In one rapidly progressing case arrest followed treatment. The three remittent cases all improved greatly. Four cases were unchanged. Of the twelve malaria treated cases with a duration of from three to four years, nine cases were improved, two very much improved and one case remained unchanged.

Habetin recommends the use of intramuscular injections of sodium nucleinate, 0.5 gram doses in 5 per cent normal salt solution, given at intervals of ten days to two weeks for five to six injections. He believes that in foreign protein therapy certain agents work better in some diseases than others and cites Wagner-Jauregg as stating that while tuberculin is effective in meta-lues, it acts badly in multiple sclerosis. Habetin reports three cases of multiple sclerosis treated with sodium nucleinate in which complete remissions took place.

Von Dollken also stresses the selective action of different proteins on various organs of the body and notes the neurotropic action of autolyzed

prodigiosus and staphylococcus vaccine, particularly in the treatment of rheumatic and diphtheritic neuritides.

The technic of applying non-specific protein therapy varies according to the agent used. In our own practice we begin treatment with the use of subcutaneous injections of typhoid vaccine (typhobacterin) for two doses, giving 250 and 500 million bacteria in the first and second doses respectively, two days apart. On the fourth day twenty-five million bacteria are given intravenously and on each succeeding fourth day intravenous injections are given of sufficient strength to raise the temperature to 101° or 102° F. An increase of one-half minim of vaccine in each dose usually gives the required amount. From eight to sixteen injections are given according to the condition of the patient. Although both Gross and Schackerl recommend the coincidental use of neosalvarsan, we preferred to use the same method as in the malarial treatment of paresis, that is, to defer drug treatment until some time after the cessation of the protein shocks.

It has been found advisable to avoid carefully the administration of too large a dosage. If too large a dose is given it is possible that the focal reaction in the central nervous system may be so severe as to endanger the patient where bulbar symptoms are present or to seriously aggravate the existing condition. In a young married woman, twenty-three years of age, with a history of a progressive spastic paraplegia of three months' duration with ataxia of both upper and lower extremities, urinary incontinence and temporal pallor of the optic disks, there was rapid improvement following the first five or six doses of the vaccine. Bladder control was reëstablished and she walked much better. About the eighth dose seven minims were given intravenously, which injection was followed by a severe chill and high fever. Severe leg pains occurred requiring morphin, (hypodermatically) for relief. The pain subsided, but urinary retention developed followed by incontinence. She later improved under treatment with sodium cacodylate. Other cases, if too large a dosage is given, do not react with the euphoria that is a sign of successful protein therapy, but complain of feeling weak, although the neurological phenomena may be improved. They likewise do not gain weight as do the more favorably influenced cases. In the case that is in poor physical condition, I believe it advisable to use minimal doses until the patient is able to note a sense of well-being the day after the treatment.

Furthermore, it has been our practice to keep our patients in bed during the treatment and to remove what foci of infection may be present. This latter step does not interfere with the vaccine therapy and may be of benefit to the general health of the patient.

Whether courses of typhoid vaccine treatment may be repeated with advantage, especially after temporary improvement and later relapse, we are unable to say, but in our opinion this should be done. Another question

that arises is whether other vaccine or protein substances may not be preferable to typhoid vaccine. Our own experience, covering twenty cases treated with typhoid vaccine, and a perusal of the literature, do not permit us to say. It is probable that the use of neosalvarsan, either concurrently or afterwards, may be of benefit.

In reporting the results obtained in the treatment of a chronic disease such as multiple sclerosis, the difficulties in arriving at a true estimate of any form of treatment are many. A large series of cases, carefully observed over an extended period of time, is necessary in order to distinguish between results of the treatment and the average rate and duration of the remissions that are characteristic of this disease. It may readily be seen that a report based upon our modest series of twenty cases treated by typhoid vaccine, must necessarily be of suggestive value only.

Of the twenty cases treated, only four were of recent onset, dating the development of symptoms two weeks, three and four months, respectively, prior to beginning of treatment. Of the remainder, the duration ranged from two to twenty years. Eight cases belonged to the chronic progressive type while the other eight were of the remitting type with a history of attacks dating back from five to twenty years.

In noting the results of treatment, these cases have been divided into three groups, remission, partial remission and no improvement. Under remission is meant marked improvement with resumption of work or of social activity. There may be residual organic signs such as increased spasticity or a slight paresthesia but the patient subjectively feels well and strong. Under partial remission is included a gain in subjective sense of well-being with a definite and persistent improvement in the objective signs such as nystagmus, ataxia or paralysis. No improvement means no change or progressive increase of the symptoms. Of the four acute cases one showed a complete remission apparently as a direct result of the treatment, one showed no improvement, and two, partial remission. Of the eight remitting cases, five showed prompt remission and three partial remission. Of the eight chronic progressive cases, seven showed no improvement and one remission.

The predominance of remissions in the remitting type suggests that the protein therapy may have had little to do with the gain and that the rest in bed and careful nursing alone may have been sufficient to cause the remission to take place. But in view of the promptness with which the remission takes place, there is at least a valid probability that the vaccine treatment had therapeutic influence.

The following case notes are given as illustrative of the three types mentioned and of the results obtained. Satisfactory accounts of the subsequent course of these cases have been difficult to obtain as most of them have been referred from a distance and the present status, therefore, could not be personally checked.

Case 1.—E. B., an Italian boy, 16 years of age, had influenza and pneumonia in 1918. In 1924 he had an acute constipation that required hospital treatment. In July, 1925, difficulty in urination began, which led to incontinence within a few days. Amblyopia occurred at the same time, leading to practical blindness within one week. Paresthesia of arm and legs associated with motor weakness occurred, and within one month a spastic paraplegia had developed.

When examined first on August 1, 1925, a marked motor weakness of all extremities and abdominal muscles of the spastic type was present. Exaggerated tendon reflexes, bilateral Hoffman and Babinski phenomena were present. An atypical Brown-Séquard syndrome from the first dorsal region down, with pain sensation absent on the right side and vibration sensibility absent on the left side, but with the sense of position unimpaired, was present. Ophthalmoscopic examination revealed a marked optic neuritis. All laboratory examinations including spinal fluid cell count, total protein content, sugar estimation, Lange gold curve, and Wassermann were negative.

On October 19, 1925, the patient was admitted to the University Hospital. The neurologic status revealed the above findings and in addition dysarthria, dysphagia, diplopia, nystagmus and cerebellar signs of ataxia. The patient was completely bedridden.

Typhoid vaccine therapy was begun. After the second injection the vision improved and his right leg was stronger. Intravenous injections were given about every four days. Usually no febrile reaction occurred, but on one occasion fever of 104° F. was present. A tonsillectomy was also performed. After six weeks the patient walked out of the hospital, subjectively well. All objective findings except the spastic signs had disappeared. Treatment was continued in the outpatient clinic until twelve intravenous injections had been given. Neurologic examination at this time showed only exaggerated patellar reflexes, absent abdominal reflexes, and at times an equivocal Babinski toe phenomenon. Eye grounds showed a mild postneuritic type of atrophy. This patient now feels entirely normal and is able to engage in athletics such as foot racing without handicap. He is working steadily as a laborer according to a recent report.

Comment.—This case showed an acute neurologic syndrome of the multiple sclerosis type with the possibility of a preceding attack the year before when he was hospitalized because of an "acute constipation." This patient might be classed as an example of encephalomyelitis disseminata. It seems to us that no clear cut distinction is possible in such cases. A complete clinical remission occurred coincident with the administration of repeated protein shocks, presumably the result of treatment. His recovery from the bedridden stage was so striking that the observers of the case were all inclined to credit treatment with aiding recovery.

Case 2.—Mrs. H. O., age 38 years, came to us on March 24, 1926. The past history was unimportant for previous infections. The onset of the illness was indefinite, but probably began about 1910 when the patient had an attack of hemianesthesia and hemiparesis both of which disappeared. Since then spells of nervous muscular jerking and difficulty in walking had been present at times, usually worse in the winter. Paresthesia had been present at times over the right side. All symptoms had been worse since January, 1926, when marked paresthesia and spastic ataxic paraplegic symptoms developed to the point of helplessness.

The neurologic findings were concentric diminution of the visual fields, exaggerated tendon reflexes of arms and legs with spastic signs, bilateral Hoffman and Babinski reflexes, absent abdominal reflexes, and moderate ataxia of the legs with diminished vibration sensibility in the legs. The patient was unable to walk unassisted; the gait was of the spastic ataxic type.

Free hydrochloric acid was absent in a three-hour fractional gastric analysis. The spinal fluid cell count was 10 per centimeter, protein content 150 milligrams per 100 c.c., Wassermann negative, the Lange gold curve was in the paretic zone.

Typhoid vaccine therapy was begun with two subcutaneous injections followed by gradually increasing intravenous injections. After the first intravenous injection fever of 102° F. resulted, and the patient had transient blindness and exacerbation of her symptoms. Within a few weeks the patient felt generally stronger and was walking about the hospital unassisted. She was receiving 4 minims of vaccine when discharged after two months' vaccine treatment.

In a personal communication from the patient on November 8, 1926, six months after cessation of treatment, she stated: "I am feeling well and I get about as good as I ever did. I see a big improvement every month. My doctor has told me my improvement is wonderful. Everybody tells me I look better than I have for years. I am gaining in weight and have started going to my clubs as always, when I was well." A recent letter states she has had no return of symptoms but describes some stiffness of her muscles in the morning, probably from spasticity.

Comment.—This case represents a very chronic intermittently progressive type of the disease, extending over a period of at least fifteen years. No hope was entertained for recovery in her condition, but it was quite apparent that treatment had in some way ameliorated her subjective symptoms and lessened the spasticity, although no objective changes were noted. According to her letter she has apparently developed a complete remission of symptoms. A report from a relative, a nurse, in September, 1928, is to the effect that her improvement has been maintained.

Case 3.—Miss L. J., age 18 years, was referred to the office on September 30, 1925. In 1918, the patient had influenza and felt weak for one year afterwards. In the spring of 1924, paresthesia and weakness were

present in the legs for two weeks. About September 20, 1925, the patient felt "grippy," and numbness appeared in the left arm. Within a week paresthesia was present in all four extremities, associated with muscular weakness and a stumbling gait.

Office examination revealed hypalgesia and hypesthesia over the dorsum of the hands, weakness of right leg muscles, especially the dorsi-flexors, indefinite patchy hypalgesia over both legs to the waist line. Diminished vibratory sensibility was present in both legs. Tendon reflexes were exaggerated and an abortive clonus with indefinite Babinski reflexes was present. The spinal fluid was normal except for a paretic Lange gold curve which was present on two examinations. While under observation in the hospital, Rosetts' induced hyperpnea test was carried out. After fifteen minutes of forced breathing definite spastic signs appeared in all four extremities. On October 11, 1925, a left third nerve palsy appeared. During a stay of several weeks silver arsphenamin injections were given with no marked improvement. She was then sent home to receive the typhoid vaccine treatment by her family physician. For one month the patient was given sodium cacodylate and iron citrate hypodermically biweekly, without apparent benefit. Then typhoid vaccine treatments were begun, and she was given fourteen injections at three-day intervals, all sub-cutaneously. An unexplained afternoon fever developed in February, 1926, so that the treatment was discontinued. The patient's family and physician felt that she was improved until the fever began, and on the whole believed the patient was improved. On April 15, 1926, the patient again came to the hospital for a six weeks' observation. A complete examination at this time showed definite objective improvement over the former exam-ination. The tendon reflexes were exaggerated and vibration sensibility was still diminished over the legs, but the epicritic sensibility, ataxia, Babinski and cranial nerve palsies were absent. Typhoid vaccine was begun intra-venously. A febrile reaction with chills, headache, fever of 101° F. and temporary exaggeration of the paresthesia occurred after the first two in-jections. The patient soon began to walk with much less ataxia and left the hospital without subjective complaints. She continued to improve and for four months after discharge continued to receive the injections until twenty intravenous injections were given. During the fall and winter of 1926, the patient remained improved.

A letter in May of 1927 tells of return of paresthesia, but the chief complaint of the patient has been gastric distress, a condition which in April, 1926, was found to be associated with a marked hyperchlorhydria and indications of gastric ulcer. The patient moved to the Pacific Coast in 1927 and her subsequent history could not be obtained.

Comment.—This case presented the typical symptoms and findings of multiple sclerosis developing after influenza. Apparently the condition was progressive, and the improvement under treatment makes one feel that

treatment was at least responsible for a temporary remission. We class her case as one showing partial remission under treatment.

Case 4.—Mrs. M., 23 years of age, was brought to the office for examination on April 29, 1928. She complained of spastic paraplegia and was barely able to walk with assistance. Since the birth of her two years old child she had had indefinite pains around her hips. In January, 1928, she developed a sciatic pain for which she was treated by a chiropractor. In February she returned to her family physician, showing an ataxic paraplegia. There had been a steady progression of the symptoms to date of examination, with the development of awkwardness in hand movements and incontinence of urine.

Neurological Examination.—Positive findings included temporal pallor of both disks, ataxia of both upper extremities to finger-nose test, vibration sensibility diminished in both wrists, absent abdominal reflexes, marked spastic weakness and ataxia of both lower extremities, loss of vibration and diminished sense of position, slight diminution of tactile and pain sensibility in the lower extremities, knee-jerks and ankle-jerks exaggerated, bilateral Babinski present. Examination of spinal fluid not allowed.

Typhoid vaccine treatment was commenced and the patient was sent home for continued treatment by her home physician. She was reported later as doing well under treatment, regaining control of the bladder and being able to walk readily without assistance. On July 9, 1928, she received, intravenously, seven minims of stock vaccine containing 2000 million of killed typhoid and paratyphoid bacteria per cubic centimeter. She developed a severe chill and very severe cramping pains in both lower extremities. Morphin, $\frac{1}{2}$ grain, was administered. Following this her paraplegia was much worse and retention of urine occurred. She required catheterization for a week and then automatic emptying of the bladder developed. Vaccine treatment was discontinued and first neosalvarsan and later sodium cacodylate was substituted. A recent report states that she has normal control of the bladder, walks up and down stairs and is feeling much better. No further neurologic examination has been made.

Comment.—This case is the only one of the series where an aggravation of the symptoms was noted as a direct result of the treatment. We have interpreted it as the result of a too severe focal reaction due to an excessively large dose of the vaccine. There had been previous improvement coincident with the commencement of the treatment. A partial remission may be assumed in this instance.

Case 5.—Mr. C. K., age 42 years, came to the office on February 18, 1926, complaining of weakness of the right arm and both legs. In 1919 the patient was critically ill with influenza for three weeks. In 1922 weakness and ataxia gradually developed in the right arm and leg. About one year ago weakness began in the left leg. Diplopia had been present at times.

The neurologic findings were vertical and lateral nystagmus, motor

weakness of the right hand, adiadokokinesis and ataxia of the right hand, exaggerated arm reflexes with Hoffman's phenomenon, sluggish abdominal reflexes, spastic weakness of the lower extremities with bilateral Babinski toe phenomena. A complete spinal fluid study was negative.

Typhoid vaccine treatment was begun in the hospital. Two subcutaneous injections of the usual prophylactic doses were followed by intravenous injections. The first febrile reaction (102.6° F.) came after the second intravenous injection. The patient was then sent home for continued treatment by his family physician. The treatments were carried out faithfully and the patient reëxamined after six months' treatment. He had received in all twenty intravenous injections and had reached the point where he no longer developed systemic reaction. There was no change in the patient's subjective or objective findings. In a personal communication from the patient November 6, 1926, he stated there was no improvement in the use of the limbs and that he had received no benefit from treatment.

Comment.—In this case there is no history of clear cut remission in the symptoms extending over a period of four years. The disease seems to be a slowly progressive condition and after a fair trial of the vaccine therapy we could see no improvement. The patient belongs to the predominantly spastic type which Schackerl states is the type most difficult to relieve.

Case 6.—Mr. J. J., age 28 years, had influenza in 1918 and one month later frequency of urination and tremor of hands. In 1920 he suffered from diplopia for one year, and also complained of dysphagia and weakness of lower extremities. In 1922 he could not walk or see well. In 1925, the condition was diagnosed as multiple sclerosis by the Veterans Bureau. Upon examination by us in June, 1926, the patient showed marked nystagmus and intention tremor, absent abdominal reflexes, spastic weakness of both legs with ataxia, bilateral clonus and Babinski, vibration sense absent up to sternum, sense of position absent left leg, analgesia right leg, precipitancy of urination. There were moderate remissions off and on, but the case on the whole steadily progressive.

Comment.—Typhoid vaccine treatment produced no objective improvement, although patient thought and still thinks he feels better, a report which is probably due to the characteristic euphoria shown by many of these cases.

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CHAPTER LVI

SUBARACHNOID HEMORRHAGE

James Charles Fox

Although Wilks, as early as 1859, described "sanguineous meningeal effusion" or "meningeal apoplexy," not until the past few years has this condition received the therapeutic attention which it deserves. The more extensive employment of lumbar puncture in various types of disorders of the nervous system has emphasized the relative frequency of subarachnoid hemorrhage as well as pointed the way to its treatment by repeated spinal drainage.

ETIOLOGY

Discussion in this article is limited to that definite clinical entity caused by the *spontaneous* rupture of a blood-vessel with bleeding directly into the cranial subarachnoid space. Arteriosclerosis is by far the commonest cause of the vascular lesion, whether the rupture takes place through a simple atheromatous erosion or a true aneurysmal dilatation. Syphilis, which plays the major rôle in aneurysm formation elsewhere in the body, is a very rare cause of intracranial aneurysm. Eppinger was the first to advocate the congenital origin of certain aneurysmal dilatations of the cerebral vessels occurring in young individuals, claiming an inherent or inborn defect in the arterial wall at points of bifurcation. The causative relationship between emboli and aneurysm formation was first demonstrated by Ponfick, and subsequent work has shown that the mechanism is not merely a weakening due to an infective arteritis but, in some cases at least, a dilatation distal to the point of occlusion by a non-septic embolus. Discussion of the various types of subarachnoid hemorrhage due to trauma does not belong here because of the surgical aspects of the problem. They must be mentioned in passing because of their relatively great frequency.

PATHOLOGY

Hemorrhage into the subarachnoid space frequently takes place through a simple atheromatous erosion of a vessel wall. The anatomical lesion leading up to the actual rupture is analogous to that characteristic of the similar process underlying cerebral hemorrhage and need not be described here. The great difference lies in the situation of the vessel involved.

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Whereas in cerebral hemorrhage the common site is in the substance of the hemisphere from one of the striate branches of the middle cerebral artery, in subarachnoid hemorrhage the blood may escape from a vessel anywhere on the surface of the brain, either from one of the cortical branches of the cerebral vessels on the surface of the hemisphere, or from one of the vessels comprising the circle of Willis, or from the basilar arteries or their branches on the brain stem and cerebellum in the posterior fossa of the skull.

Intracranial aneurysm, although only occasionally manifesting itself clinically and even more rarely diagnosed, is not an uncommon pathological finding, occurring in more than 1 per cent of postmortem examinations of the brain. Arteriosclerotic degenerative changes, leading to either a saccular or fusiform dilatation, constitute by far the commonest cause. The exact histopathology of the "juvenile" aneurysmal formation has never been satisfactorily explained, some claiming a mycotic origin rather than an inherent defect in the wall. Whatever the etiological factor, there is a striking predilection for the formation of aneurysms at the points of junction and bifurcation of the arteries comprising the circle of Willis. This is especially true of the intracranial portion of the internal carotid at the point of parting to form the anterior communicating branch.

Hemorrhage into the subarachnoid space may take the form of a sudden rupture with gradual arrest of bleeding or have the character of slow intermittent leakage. In the case of aneurysm, the ruptured sac or its extravasated clot may directly compress neighboring structures and produce focal irritative or paralytic symptoms. However, the meningeal irritation produced by the presence of the blood in the subarachnoid space is the most important feature of the situation. Because of the free communication of the cranial and spinal subarachnoid spaces with the basal cisterns, a widespread meningeal area is brought into direct contact with the bloody cerebrospinal fluid, whose irritative effect is thus magnified.

Bagley has recently shown that even when small amounts of blood are experimentally introduced into the subarachnoid space of young and adult dogs, a reaction of the parts of the meninges which have come into contact with the blood, takes place. This tends to subside with the disappearance of the blood from the fluid. However, a relatively large amount of fibrous tissue remains, especially in those cases subjected to repeated injections. In addition to the meningeal thickening occurring over the cortex or at the base, actual alterations of cortical structure and dilatation of the ventricles were occasionally noted as later pathological changes.

Of course, it must be mentioned that hemorrhage into the substance of the brain may find its way indirectly into the subarachnoid space, either by way of the ventricular system or by breaking through onto the surface of the hemispheres. Also in cerebral thrombosis, especially when this occurs in the neighborhood of the large cisterns at the base of the brain,

a certain amount of blood from the ruptured capillaries of the involved area escapes into the adjacent subarachnoid space. Neither of these conditions constitutes subarachnoid hemorrhage in a true sense as implied in this article.

SYMPTOMS

Whenever an aneurysm or diseased blood-vessel suddenly ruptures into the subarachnoid space the symptomatology is fairly constant and dramatic. The patient experiences a sudden stabbing pain in the head or back of the neck, a sensation which he subsequently describes as though "something snapped or cracked inside the head." Loss of consciousness is variable. When it does occur it is usually delayed for several minutes. During this period the patient suffers increasingly agonizing headache, usually associated with pains radiating into the neck, spine, and back of the shoulders and hips. There is a feeling of giddiness and weakness, frequently blurring of vision, and soon afterwards vomiting, which may or may not be projectile in type. Some degree of mental clouding later makes its appearance, varying from slight mental confusion and drowsiness to deep coma. Convulsive seizures may supervene at this stage, but they are the exception rather than the rule, and are usually of the tonic type. The apoplectic type of onset indicates a major rupture. The more gradual development of symptoms indicates a slow leakage and, in some instances, there is no clinical manifestation of the actual beginning of bleeding.

PHYSICAL SIGNS

The clinical findings at this stage and subsequently may be conveniently described under two headings: (1) General, related to the meningeal irritation and increased intracranial pressure; (2) focal, dependent upon the type and location of the vascular lesion.

Stiffness of the neck, retraction of the head and positive Kernig test, are universally present to some degree but vary as to their onset, intensity, and duration. The characteristic temperature chart is one of irregular fever rising to 101° F., rarely above 102°-103° F., and persisting for ten to fourteen days. The pulse is variable but tends to bradycardia, likely to hover around 60 during the early days of the illness. The respirations are variable in character, except in the comatose state, when they are Cheyne-Stokes in nature. The fundi usually show some degree of engorgement of the retinal veins and blurring of the optic disks. The deep reflexes are likely to be exaggerated at first, subsequently diminishing and often disappearing altogether. The plantar responses are equivocal or extensor in type. The mental state remains clouded and confused, with alternating periods of drowsiness and irritability, occasionally verging into mild delirium.

Focal manifestations may or may not appear, depending upon the site of the lesion, the size of the extravasated clot, and other factors not clearly understood. The neurological picture will obviously depend upon the locus of compression. Because of the relative frequency of the aneurysmal lesion at the circle of Willis at or near the bifurcation of the internal carotid, the resultant syndrome merits description. In addition to the meningeal type of headache, sharp recurrent bouts of pain in the eye and frontal region on the side of the lesion are quite characteristic. There may also be an associated hypo-esthesia in the corresponding upper trigeminal area with loss of the corneal reflex. The adjacent optic nerve is directly compressed, causing severe impairment of vision in the involved eye. Frequently the blood is forced around the sheath of the nerve, appearing in the retina as a characteristic blood droplet near the disk, which is also engorged. Perhaps the most characteristic feature of all is the unilateral oculomotor palsy causing diplopia, divergent squint, ptosis, and varying degrees of weakness of the related ocular movements. The pupil is dilated and non-reactive. In combination with the disturbance of the cranial nerves there may or may not be a contralateral pyramidal disorder (Weber's syndrome) depending upon the degree of compression of the neighboring peduncle. Proptosis of the eye on the side of the lesion has been frequently described. A bruit is rarely heard upon auscultation over the skull in intracranial aneurysm. Focal symptoms gradually disappear but there is a strong likelihood of a neurological residuum, especially as regards the disordered function of the second and third cranial nerves.

CEREBROSPINAL FLUID

The spinal fluid is absolutely characteristic in all cases in that it contains an admixture of blood or the products of its disintegration. The findings depend upon the length of time that has elapsed between the hemorrhage and the lumbar puncture. Within the first few hours the fluid will be diffusely or increasingly bloody in appearance if collected in successive portions. The supernatant fluid on standing or after centrifugalization has a slight but definite yellow tinge, usually within a very few hours (eight to twelve) from the time of bleeding. The number of red blood-corpuscles varies with the severity of the hemorrhage from a few thousand to over a million per c. mm., but in the author's experience averages about 50,000. Within twenty-four hours hemolysis has progressed and the color of the supernatant fluid has become a canary or amber yellow. Within a week to ten days the red cells have usually completely or nearly disappeared and the so-called xanthochromia is at its height. In the absence of fresh hemorrhages, the yellow color gradually disappears until, at the end of three weeks, the spinal fluid has usually returned to normal.

The presence of blood in the subarachnoid space acts as a meningeal irritant, causing a mild pleocytosis in addition to the number of white blood-corpuscles present as a normal constituent of the admixed blood. This pleocytosis is both relatively and actually increased as hemolysis progresses. The tests for globulin show a slight increase. The amount of total protein is also slightly above normal. However, it is rare to find above 100 milligrams per 100 c.c. The other chemical constitutents show no significant variation. The Wassermann test is usually but not invariably positive when the etiological basis for the vascular lesion is syphilitic. The colloidal gold test is unsatisfactory because of the presence of blood.

The pressure of the cerebrospinal fluid, as determined by a manometer attached to the needle in the lumbar space with the patient in the horizontal position, is almost invariably above normal. In the early stage the reading may be as high as 300 to 400 millimeters of spinal fluid. Subsequently, with the gradual disappearance of the more acute symptoms of increased intracranial pressure, the pressure falls to normal (100 to 150 millimeters) or may remain slightly above normal even after the fluid itself has become clear.

DIAGNOSIS

The abrupt onset of pain in the head, but without immediate loss of consciousness, followed by symptoms of meningeal irritation, but without hemiplegic disorder, points at once to the meningeal rather than the cerebral form of apoplexy. Moreover, hypertension or arteriosclerosis need not characterize the clinical picture, because hemorrhage into the subarachnoid space may take place in a young person as the result of the rupture of an inherent aneurysmal defect of a vessel, which had previously given no clinical warning.

When the onset is less dramatic, due to slow leakage rather than sudden rupture, the clinical picture frequently simulates that of meningitis. In fact, the incorrect provisional diagnosis of tuberculous or meningococcus meningitis is likely to be made, until the finding of blood rather than pus in the spinal fluid indicates the error. While the spinal fluid findings are decisive in each instance, the following points may be helpful in the differential diagnosis. In hemorrhage the temperature is irregular, averaging 101° F., rarely above 102° F.; the pulse is usually below normal, often around 50; the respirations are variable, frequently shallow. In meningitis the fever is usually high (104° F.) and constant; the pulse is apt to remain above 100; the respirations are usually accelerated. The constitutional symptoms are likely to be more severe in meningitis especially the mental manifestations, whereas drowsiness alone may characterize the presence of blood in the subarachnoid space. Cranial nerve palsies are common to both, but the unilateral oculomotor palsy is the more characteristic of hemorrhage. Retinal congestion may accompany

both conditions, but the presence of blood-droplets in the retina, especially if unilateral, points to hemorhage. In meningitis the course is usually progressive; in hemorrhage the course is usually one of slow improvement unless characterized by exacerbations related to recurrent bleeding. A history of a previous similar episode with recovery is of course strongly in favor of hemorrhage.

PROGNOSIS

While always uncertain, the prognosis in general is favorable for slow recovery, as resolution of the clot and absorption of blood gradually take place. This is particularly true in the group of cases of spontaneous rupture occurring in young individuals. In all cases of aneurysm, whether in the congenital or arteriosclerotic group, there is a strong tendency to a repetition of rupture, sometimes after many years' interval. The outlook in each successive attack becomes less favorable, because of the greater likelihood of either immediately fatal hemorrhage, or uncontrolled oozing, or recurrent leakage taking place. The association in the atheromatous cases, of extreme hypertension and especially of renal disease speaks relatively uniformly for a rapidly fatal outcome.

When recovery from the immediate attack takes place, impairment of the intellectual faculties is less likely to follow than in the case of cerebral hemorrhage. Sequelæ occasionally take the form of difficulty in concentration, defects in memory, and disturbances of judgment. However, not infrequently, there is a permanent change in the personality following the initial subarachnoid hemorrhage, which is likely to become more marked following each subsequent attack. The patient may show less energy and interest in his former affairs; he often becomes irritable and subject to fits of depression, which he is wont to associate with bouts of headache, dizziness or a "peculiar sensation inside the head."

TREATMENT

Although lumbar puncture was formerly looked upon as a dangerous procedure following cerebral vascular accidents of all sorts, during the past few years the value of spinal drainage in the treatment of hemorrhage into the subarachnoid space has become generally recognized. Conservative employment under proper technical control results, in most cases, in a striking relief of the symptoms caused by the meningeal irritation. Because of the vicious cycle set up by the presence of blood in the subarachnoid space, causing an increase, first in cerebrospinal pressure and then in intracranial blood-pressure, it is possible that occasionally artificial removal of the irritating substance may have a secondary favorable influence on the reparative course of the vascular lesion.

Of course it is obvious that there must be no sudden drop in the cere-

brospinal fluid pressure which might promote a fresh rupture and renewed bleeding. Guillian has also warned against withdrawing fluid soon after the occurrence of the hemorrhage; that is, before the process of repair of the rent in the vessel is well under way. Obviously, if the focal signs point to a leaking aneurysm, especially one localized in the posterior fossa, spinal drainage is contra-indicated. Although the procedure must be adapted to the circumstances of each individual case, the following technic and principles are suggested for general guidance.

Lumbar puncture is performed (not earlier than twenty-four hours after the hemorrhage) with the patient in the horizontal position. A needle with a two-way stopcock is used, to one of which a manometer remains attached throughout the procedure. After obtaining the initial reading, the bloody fluid is allowed to escape very slowly through the free opening. The drainage is frequently interrupted by manometer readings and is entirely stopped when the pressure has reached a level approximating normal (100 to 150 millimeters). Usually this is accomplished after the removal of from 10 to 20 c.c. of bloody fluid. The frequency of the drainage is determined by the intensity of the symptoms of meningeal irritation. These tend in many cases to recur in milder form on the day following the drainage. Optimum results can be obtained by daily drainage of small quantities, at the same time avoiding the risk of disturbance of intracranial pressure relations caused by more copious but less frequent withdrawals. Upon the disappearance of meningeal irritative symptoms, spinal drainage is discontinued. This is usually coincident with the disappearance from the spinal fluid of the products of blood-disintegration.

Contra-indications to repeated drainage are twofold: (1) the appearance of characteristic apoplectic symptoms soon after the drainage, indicating renewed rupture and bleeding; (2) a continually higher content of red blood-cells in fluid withdrawn at successive drainages, indicating uncontrolled leakage. However, it is well known that recurrent bleeding occurs occasionally over a short period of time in the undrained case. Certainly the benefit obtained counterbalances the risk entailed, providing proper pressure control is employed.

In case the history is that of recurrent attacks and the neurological picture points to focal pressure in the region of the internal carotid artery at a point near its bifurcation, the assumption of a leaking aneurysm is justified and surgical treatment should be considered. In a recent article by Birley, Trotter strongly advocates ligation of both the internal and external carotid arteries just above the bifurcation of the common carotid, in this way giving the fullest possible control of blood to the aneurysm. It should be added that a preliminary trial ligation of the exposed vessels should be first carried out to test the efficiency of the collateral circulation of the circle of Willis.

As far as general measures are concerned, the lateral recumbent

posture allowing retraction of the neck, the liberal use of pyramidon, and the application of ice-bags to the head and neck, seem to be the most effective in alleviating the headache. Bloodletting seems advisable in the markedly hypertensive and plethoric individual, but should be used with caution. Complete rest in bed for at least two weeks after the disappearance of symptoms should be insisted upon. The period of convalescence should be prolonged. As a prophylactic measure, the patient should be warned against the danger of any form of sudden exertion.

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CHAPTER LVII

THE TREATMENT OF EPILEPSY IN CHILDHOOD

M. G. Peterman

GENERAL CONSIDERATIONS

The treatment of idiopathic or essential epilepsy in childhood should begin with a thorough understanding of the disease. The earlier proper treatment is begun, the more effective will it be and consequently, the more gratifying will be the results. When the disease has become established in the adult, treatment is mainly symptomatic; in the child it may be hoped to reorganize the metabolism, readjust the reactions, as well as relieve the symptoms before the disease has produced a demoralizing effect on the psyche if not a pathologic lesion in the brain.

Idiopathic or essential epilepsy is a chronic disease of the nervous system characterized by periodically recurring convulsions, lapses, or abnormal mental states occurring in an individual with a constitutional inferiority or personality defect, but with no demonstrated pathologic lesion. In this chapter we are concerned only with the treatment of idiopathic or essential epilepsy as distinguished from jacksonian or focal epilepsy, or from epileptiform convulsions caused by organic lesions such as brain tumor, cerebral hemorrhage, cerebral birth palsy, and encephalitic residue.

Epilepsy may begin at any age, but it is not common before the first year of life. In the majority of epileptics, the onset of the disease occurs before puberty. About half of the epilepsies in children begin as petit mal; the other half as grand mal. The majority of untreated cases of petit mal gradually develop grand mal attacks. Psychic equivalents are rare as is pyknolepsy. In almost half of the parents of the epileptics there may be obtained a history of migraine, nervousness, emotional instability, insanity, asthma, or chronic alcholism. Epilepsy is found in about 10 per cent of the patients' families, but it is at least one generation removed; that is, it is found in cousins, uncles, aunts, and grandparents. The inheritance of a nervous system defect is usually evident. Thus the patient is born a potential epileptic, but the exciting cause of his convulsions is probably a disorder in metabolism, recurring periodically. The suggestion of a metabolic disorder is based upon a number of consistent observations. There is usually a history of constipation, and purging is of benefit in

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treatment. There is a close relation between the attacks and dietary indiscretions; regulation of the diet is very beneficial and fasting is usually effective in controlling the convulsions. The appetite is often capricious and there is a tendency to bolt food. In some cases, associated with the attacks, there occurs emesis of undigested food taken twenty-four to thirty-six hours previously.

The psychic factor is very important in the precipitation of seizures, especially petit mal. Irritating factors in the home, conflicts with brothers or sisters, with parents or relatives, when these occur frequently, greatly increase the number of attacks. Harsh discipline, unusual excitement, irregular hours, lack of rest and sleep, may also aggravate the condition.

GENERAL MANAGEMENT

It is well known that change of environment exerts a favorable effect on epileptics. These children seldom have an attack in the physician's office or during the first few days in the hospital. They are often free of seizures during the first week or more of a visit to new surroundings. When possible, the first step in management should be a complete change of environment; a hospital or sanatorium is advisable if there is no convenient country place or distant home. The immediate family should be kept away from the patient.

Secondly, the disease epilepsy and fear of convulsions should be banished from the child's thoughts. He must be taught that he is a healthy, normal individual and he must never consider himself a patient. The child should not be conscious of observation but should be allowed normal play and exercise with reasonable moderation.

Thirdly, there should be established a regularity in the daily regimen. The three meals should be equally divided and should be given at the same time every day. There should be a half hour rest period before the noon and before the evening meals. Each meal should consume twenty to thirty minutes during which time the food should be thoroughly chewed and slowly swallowed. A half hour quiet period should follow each meal, and at noon this should be extended to at least one hour of complete relaxation in a quiet, darkened room. Children under ten years of age should be put to bed at 7:30 P.M.; those from ten to fifteen at 8:30 P.M. They should be allowed to sleep until they awaken.

Fourthly, there must be a regular, daily habit time, and if necessary, cathartics should be given to insure a daily bowel movement.

TREATMENT

With the above management we may consider special treatment. This will depend upon a number of factors, more especially the patient's age,

duration of the disease, frequency and severity of seizures, and previous treatment.

When the diagnosis of epilepsy is made, the treatment should be vigorous and thorough, and should be continued for at least one year, better, two years, after all symptoms have ceased. The treatment should begin with the general measures outlined above. Further therapeutic procedure will depend upon the family economic situation, and upon the facilities available. It is useless to start an expensive detailed procedure, such as the ketogenic diet, if this procedure cannot be continued for a long period of time.

It must be impressed upon the child and his parents that any treatment, to be successful, requires the coöperation of the entire family, and requires strict adherence to the regimen outlined. A great many patients will show definite improvement with no further treatment than the general management described above.

The next step in therapeutics will be a regulation of the diet. If the circumstances and facilities are such that the ketogenic diet may be continued throughout a period of two years or more, it is advisable that this be begun immediately. The ketogenic diet is described in detail below. In milder cases with convulsions which occur only four or five times a year, and in those cases in which circumstances do not permit the ketogenic diet, it is advisable to start treatment with the restricted diet.

The Restricted Diet

The restricted diet consists of the following:

Fruits.—Ripe bananas, grapefruit, and oranges may be given raw; one orange, or half a grapefruit, once a day; one banana, not over twice a week.

Children under three years of age should receive, perhaps, one-half these amounts. The other fruits should be thoroughly stewed or baked, and if preserved, they should be cooked or packed without sugar. The list should be restricted to apples, apricots, figs, peaches, pears, pineapples, plums, prunes, rhubarb, and tomatoes.

Vegetables.—All vegetables should be cooked until soft, except lettuce, celery, or watercress, which may be given raw, but thoroughly minced. The selection should be restricted to asparagus, beets, cabbage, cauliflower, celery, eggplant, parsnips, spinach, and turnips.

Grains or Cereals.—These are limited to oatmeal and whole wheat preparations, which should be thoroughly cooked or steamed. Bran preparations may also be given once a day, either cooked or prepared.

Bread.—Well-baked bread, at least twenty-four hours old, may be given with or without toasting. This should be bran bread, rye bread, whole wheat bread, or bran muffins.

Milk Products.—Fresh butter should be given in as large amounts as the child will take. Buttermilk may be given twice a week; cottage cheese, two or three times a week; cream with each meal. The cream should be at least 20 per cent fat, and preferably with as high a fat content as the child will take.

Eggs.—Eggs may be given in any form; children under five receiving one egg a day; children over five, two or three.

Meats.—Bacon should be fried crisp. All other meats should be roasted, baked, broiled or boiled, until tender. The variety is restricted to lamb, veal, kidneys, liver, sweetbreads, any poultry, and codfish, mackerel, salmon, trout, whitefish, and pike.

Soups.—Children under five years of age may have from six to eight ounces of soup once a day. Children over five may be given from eight to ten ounces once or twice a day. The soup is restricted to vegetable soup, beef broth, celery soup, chicken broth, and cream soup.

Beverages.—These are restricted to chocolate or cocoa, made with milk and served with cream, fruit juices, mineral water, orangeade, lemonade, and grape juice. The fluid intake should be restricted to a minimum.

Appetizers.—Appetizers such as olives, mushrooms, and pickles, are not allowed, nor are the condiments allowed, except for salt and vinegar to season. Honey and syrup are allowed in moderation, but a minimum of sugar is to be used.

Desserts.—These are restricted to ices, ice cream, jams, jellies, and preserves.

All foods which are not mentioned are not allowed. The amount prescribed for each individual is the average helping allowed for a child of that age.

Drugs

Drugs are simply an adjunct in the treatment of epilepsy. It must always be kept in mind that drug treatment alone will not be highly successful. However, if the patient has been given the proper attitude, if he will be restricted to a certain daily regimen and a properly prepared diet, certain drugs will be of considerable benefit in the control of the grand mal. There is no drug known which will influence the petit mal convulsion.

The drugs of therapeutic value are limited to the barbital series; *phenobarbital* for older children and *phenobarbital sodium* for children under three years of age, are the most commonly used preparations. The other new preparations of the barbituric acid series may also be used. *Bromids* are used only as a last resort when the convulsions persist and the prospects of obtaining mental rehabilitation are not good.

It has been demonstrated that all patients acquire a tolerance for the bromids, and that certain patients have an idiosyncrasy for this drug.

Continued use of bromid results in a depletion of the body chlorids, and eventually may produce a mental deterioration.

The dosage of phenobarbital will depend entirely upon the age of the child and the frequency of the convulsions. The time of administration of the drug is entirely dependent upon the time of the appearance of the convulsion. Once a convulsion has begun, the only treatment which will abort or stop the seizure is a complete anesthesia. Chloroform produces the quickest results. Infants up to three years of age may be given ¼ grain of phenobarbital, from one to three times in twenty-four hours; children from three to five years of age may be given ½ grain, from two to four times in twenty-four hours; children from five to ten years of age may be given ¾ grain, two or three times a day; and, children from ten to fifteen years of age may be given 1 or 1½ grains of the drug, two to four times in twenty-four hours, as indicated.

The patient should be given enough phenobarbital to keep the convulsion under control. The drug should be given six to twelve hours before the anticipated attack. Once the convulsions are kept under control, the dosage of drug should be kept the same for at least six months, unless untoward reactions intervene. There have been very few unfavorable reactions reported, with even large doses of phenobarbital. A child six years of age has been given six grains for a period of five months with no harmful effects observed.

The occasional reactions, simulating measles, which occur in a small number of patients susceptible to the drug, may be easily controlled by discontinuing the phenobarbital for a short period of time, or by substituting one of the other preparations.

The Ketogenic or High Fat Diet

The influence of fasting and purging on the convulsions of epilepsy was known to Hippocrates and the Ancients. Guelpa and Marie reported favorable results in the treatment of epilepsy with fasting, in 1910. Geyelin was probably the first physician in America to report the results of starvation in epilepsy.

It has been demonstrated that starvation or fasting greatly influences the convulsions of epilepsy and controls the attacks in the majority of children. There are certain cases of epilepsy in which starvation produces the opposite effect, and it has been demonstrated that certain children develop convulsions whenever the blood-sugar reaches a low level. However, in most patients, a fasting diet will produce a marked decrease in the number and in the severity of the attacks.

The details of the changes which occur are referred to in the literature. It was on the basis of the results produced in fasting and starvation that the ketogenic or high fat diet was instituted. In the original publication,
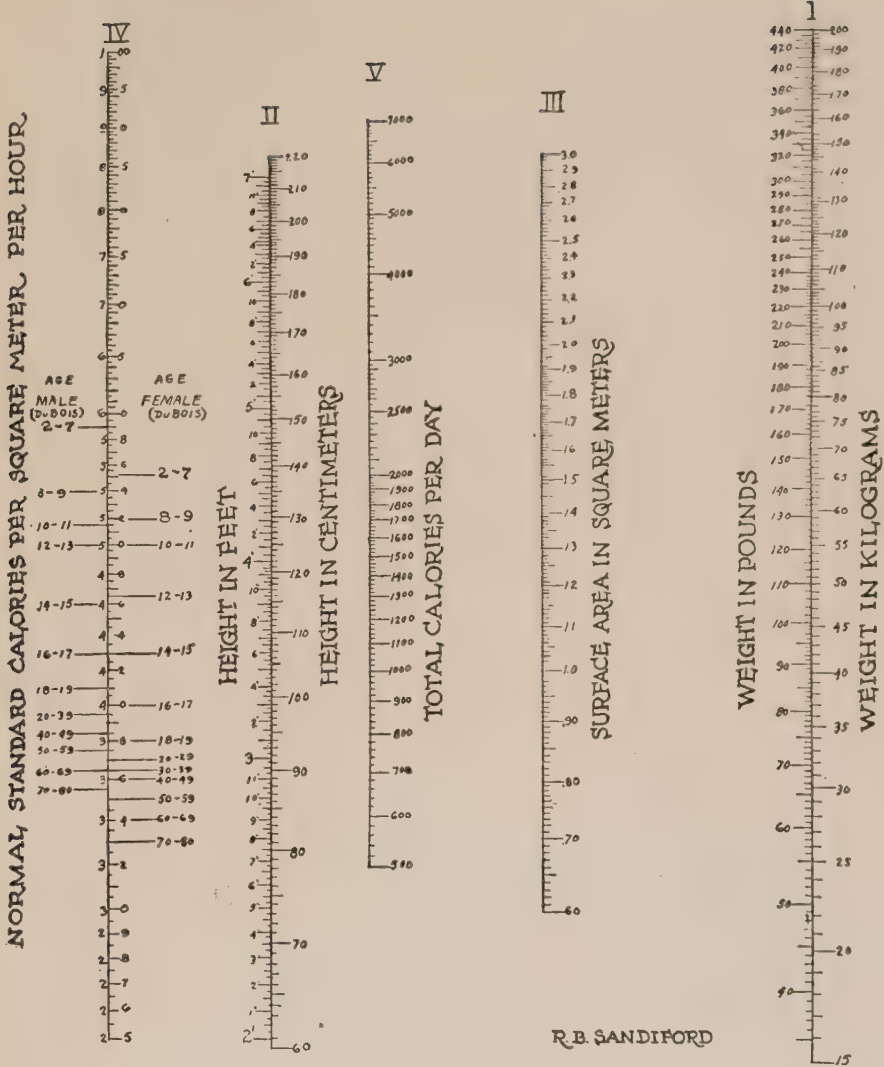
Fig. 1.—Diabetic Diet Chart.

Place the chart on a flat smooth table. Use only a ruler with a true straight edge. Do not draw lines on the chart but merely indicate their positions by the straight edge of the ruler. Locate the various points by means of needles (pin stuck through the eraser of a lead pencil). Locate the patient's weight on Scale I and his height on Scale II. The ruler joining these two points intersects Scale III at the patient's surface area. Locate the age and sex of the patient on Scale IV. A ruler joining this point with the patient's surface area on Scale III crosses Scale V at the required total food calories for basal maintenance.

it was suggested that the results of the ketogenic diet might be due to the acidosis and ketosis produced. It has subsequently been demonstrated that there is no acidosis; rather, simply a tendency toward acidosis. The high fat, modified protein, low carbohydrate diet produces a disturbance of the acid base balance and a ketosis, the degree of which will depend upon the fatty acid-glucose ratio. Ketosis alone or acidosis alone do not control the seizures.

The ketogenic diet is best instituted in a hospital or sanatorium, where there may be enlisted the aid of a competent dietitian. The treatment is begun with a preliminary period of starvation of one week or ten days. During this period, the patient is given the juice of one orange, six to sixteen ounces of diabetic broth, and one to six bran wafers with each meal. Water is allowed freely. At the end of one week, or after the convulsions have stopped, the patient may be abruptly placed on the proper diet prescribed.

This prescription consists of from 10 to 15 grams of carbohydrate, 1 gram of protein per kilogram of body weight, with the remaining caloric requirements supplied in fat. The metabolic requirement may be determined by the Sandiford table, or it may be roughly calculated at 30 calories per pound. The total calories allowed should not exceed 2200.

The fat is increased, if necessary, to keep the patient's weight at or slightly below normal for his age and height. Also, the fat may be increased to 10 to 15 grams, every four days, until the convulsions cease. Any tendency to nausea or vomiting can be easily controlled with 6 to 8 ounces of orange juice, served ice cold.

About the fifth or sixth day of fasting, acetone and diacetic acid are to be found in the patient's exhaled air, in the blood and urine, and will continue to be present when the patient is taking the high fat diet.

The urine tests are made with ferric chlorid (10 per cent iron). One half c.c. is added to 2 c.c. of urine. The brown, red, or purple color indicates the presence of acetone. It must be remembered that the phenol compounds, salicylates, antipyrin, and other drugs, may produce a red color. The reaction produced with these drugs will not disappear with heating, as will the reaction produced by acetone and diacetic acid. A negative reaction usually means that extra carbohydrate has been taken. The urine should be tested every morning, and a complete examination should be made once a week.

In computing this diet, all the vitamins must be provided for as well as the minerals. Since the diet usually contains proportionately large amounts of 3 per cent vegetables for bulk, and of the 10 per cent fruits, whole wheat, butter, and cream, the vitamin requirement is easily fulfilled. The grains, meats, and fish will supply the minerals.

There have been several attempts in the literature to make the diet prescription calculation a difficult problem. Formulæ and tables are pre-

sented in an array made formidable to the average physician. There is absolutely no justification for the attempt to make the calculation of the diet prescription difficult. The carbohydrates, in the beginning, must be reduced to the absolute minimum. This figure may be assumed to be, arbitrarily, 10 to 15 grams. The proteins must also be reduced to a minimum, consistent with a positive nitrogen balance. One gram of protein per kilogram is a safe allowance, and if results are not satisfactory, this amount may later be reduced, in children over five years of age, to two-thirds of a gram per kilogram of body weight. With the amounts of carbohydrates and protein thus established, enough fat is added to keep the patient's weight at, or slightly below, normal for his age and height. Since the diet is further adjusted according to the individual patient's reaction, there is no object in calculating the original prescription with a slide rule.

Information, concerning foods and food values, is available to the physician and to his patients in a number of small Diabetic Primers.

Epileptics are usually constipated, and following a period of starvation, the ketogenic diet usually produces a further constipation. It is desirable to insure a free bowel movement every day. The patient may either be given a preparation of agar-agar in mineral oil before breakfast and again before the evening meal in sufficient amounts so that after four or five days there results a daily evacuation; or the patient may be given a saline cathartic, preferably Carlsbad salts, before breakfast, following the day when there has been no stool.

The necessary salt for seasoning is allowed, but no further salt, pepper or other condiments are provided. The food should be rather equally divided into the three meals of the day. The patient must eat all of the food in order to maintain the desired equilibrium. This diet, when properly arranged with the correct allowance for vitamins and the necessary mineral salts, will provide adequate food material for energy, normal growth, and development. It has not been a difficult matter to keep most of the children in ketosis. The coöperation of these young patients is usually excellent. If there is considerable hunger, the bulk of the diet may be increased with bran products, agar-agar, jelly, and gelatin to satisfy the appetite. The fluid intake is restricted to a minimum.

A list of the chemical composition of the most commonly used food materials is appended; also, a list of the most useful diabetic foods, and some recipes for the preparation of others.

Food Materials	Per Cent per 100 Grams		
	Protein	Fat	Carbohydrates
Fruits			
Apples	.4	.5	14.2
Apricots	1.1	...	13.4
Bananas	1.3	.6	22.0
Figs	1.5	...	18.8
Grapefruit	1.	...	10.
Oranges	.8	.2	11.6
Peaches	.7	.1	9.4
Pears	.6	.5	14.1
Pineapple	.4	.3	9.7
Plums	1.0	...	20.1
Prunes	.9	...	18.9
Rhubarb	1.3	.1	5.8
Tomatoes	.9	.4	3.9
Vegetables			
Asparagus	1.8	.2	3.3
Beets	1.6	.1	9.7
Cabbage	1.6	.3	5.6
Cauliflower	1.8	.5	4.7
Celery	1.1	.1	3.3
Eggplant	1.2	.3	5.1
Lettuce	1.2	.3	2.9
Parsnips	1.6	.5	13.5
Spinach	2.1	.3	3.2
Turnips	1.3	.2	8.1
Grains or Cereals			
Oatmeal	2.8	.5	11.5
Bread			
Rye	9.0	.6	53.2
Whole wheat	9.7	.9	49.7
Milk Products			
Butter	1.0	85.0	...
Buttermilk	3.0	.5	4.8
Cottage cheese	20.9	1.0	4.3
Cream	2.5	18.5	4.5
Milk	3.3	4.0	5.0
Eggs			
Uncooked	13.4	10.5	...
Boiled	13.2	12.0	...
Meats			
Bacon, uncooked	9.9	67.4	...
crisp	20.0	50.0	...
Kidneys, beef	16.6	4.8	.4
mutton	16.9	12.6	...
pork	15.5	4.8	...
veal	19.0	5.3	...
Liver, beef	20.4	4.5	1.7
mutton	23.1	9.0	5.0
pork	21.3	4.5	1.4
veal	19.0	5.3	...

Food Materials	Per Cent per 100 Grams		
	Protein	Fat	Carbohydrates
Meats (continued)			
Sweetbreads	20.2	9.5	...
Poultry, chicken	21.5	2.5	...
fowls	19.3	16.3	...
goose	13.4	29.8	...
turkey	21.1	22.9	...
Codfish	16.5	.4	...
Mackerel	18.7	7.1	...
Pike	17.9	.8	...
Salmon	22.0	12.8	...
Trout	19.2	2.1	...
Whitefish	22.9	6.5	...
Soups			
Celery	2.2	.1	.2
Chicken	3.6	.1	1.5
Vegetable	2.9	...	.5
Beverages			
Chocolate	12.9	48.7	30.3
Cocoa	21.6	28.9	37.7
Desserts			
Honey	8.0	46.0	3.0
Ice cream	.4	...	81.2
Jellies and preserves, apples, crab	.3	2.4	54.4
apricots	.9	...	17.3
apricot sauce	1.9	1.3	48.8
cherries	1.1	.1	21.1
cherry jelly	1.1	...	77.2
peaches	.7	.1	10.8
pears	.3	.3	18.0
prune sauce	.5	.1	22.3
strawberries, stewed....	.7	...	24.0
tomato preserves	.7	.1	57.6

Atwater and Bryant, "The Chemical Composition of American Food Materials," United States Dept. of Agriculture, Bulletin No. 28 (Rev. Ed.).

MENUS

Following is a list of menus for one week, for a patient weighing twenty-five kilograms or fifty-five pounds. The diet prescription in this case was carbohydrate, 15 grams, protein, 25 grams, fat, 182 grams. This prescription allowed 32 calories per pound, or about 72 calories per kilogram.

SUNDAY

Breakfast

        30 grams of 10 per cent fruits [1]
        1 egg—scrambled
        25 grams of bacon (fat)
        50 grams of 32 per cent cream
        20 grams of butter

Dinner

        75 grams of 3 per cent vegetables [2]
        50 grams of 32 per cent cream
        40 grams of butter
        25 grams of bacon (fat)

Supper

        75 grams of 3 per cent vegetables
        30 grams of 10 per cent fruits
        50 grams of 32 per cent cream
        45 grams of butter
        36 grams of chicken (18 dark, 18 white)

Food Value

Carbohydrate :15   Protein :25.1   Fat :182

Food	Grams						
	Morning	Noon	Evening	Total	Carbohydrates	Protein	Fat
Vegetables, 3 per cent	..	75	75	150	4.5	1.5	...
Fruit, 10 per cent	30	..	30	60	6.	.6	...
Eggs	1	..	..	1	..	6.	6.
Cream, 32 per cent	50	50	50	150	4.5	3.	48.
Butter	20	40	46	106	..	..	89.3
Bacon (fat)....	25	25	..	50	..	5.	33.3
Chicken	..	..	36	...	..	9.	5.4

[1] Grapefruit, lemons, oranges, cranberries, strawberries, blackberries, gooseberries, peaches, pineapple, watermelon.

[2] Lettuce, spinach, asparagus, rhubarb, endive, marrow, sorrel, sauerkraut, beet greens, dandelion greens, swiss chard, celery, tomato, brussel sprouts, water cress, sea kale, cauliflower, egg plant, cabbage, string beans, broccoli, mushrooms.

MONDAY

Breakfast

      30 grams of 10 per cent fruits
       1 egg—scrambled
      50 grams of 32 per cent cream
      20 grams of butter
      40 grams of bacon (fat)

Dinner

      75 grams of 3 per cent vegetables
      50 grams of 32 per cent cream
      30 grams of butter
      22 grams of meat (cooked)

Supper

      75 grams of 3 per cent vegetables
      30 grams of 10 per cent fruits
      50 grams of 32 per cent cream
      30 grams of butter
      44 grams of bacon (fat)

FOOD VALUE

Carbohydrate :15   Protein :25   Fat :182.3

Food	Grams				Carbo-hydrates	Protein	Fat
	Morning	Noon	Evening	Total			
Vegetables, 3 per cent	..	75	75	150	4.5	1.5	....
Fruit, 10 per cent...	30	..	30	60	6.	.6	....
Eggs	1	..	..	1	..	6.	6.
Cream, 32 per cent..	50	50	50	150	4.5	3.	48.
Butter	20	30	31	81	..	..	68.8
Bacon (fat)	40	..	44	84	..	8.4	56.28
Meat (cooked).....	..	22	..	22	..	5.5	3.3

TUESDAY

Breakfast

 30 grams of 10 per cent fruits
 50 grams of 32 per cent cream
 30 grams of bacon (fat)

Dinner

 50 grams of 3 per cent vegetables
 1 baked egg with cheese (Recipe 1)
 40 grams of butter
 50 grams of 32 per cent cream

Supper

 67 grams of 3 per cent vegetables
 30 grams of 10 per cent fruits
 43 grams of butter
 50 grams of 32 per cent cream
 32 grams of bacon (fat)

FOOD VALUE

Carbohydrate :15   Protein :25   Fat :182

Food	Grams				Carbo-hydrates	Protein	Fat
	Morn-ing	Noon	Eve-ning	Total			
Vegetables, 3 per cent	..	50	67	117	3.5	1.2	...
Fruit, 10 per cent...	30	..	30	60	6.	.6	...
Baked egg with cheese	..	R1	..	...	1.	14.	22.
Butter	..	40	43	83	..	..	70.5
Cream, 32 per cent..	50	50	50	150	4.5	3.	48.
Bacon (fat)	30	..	32	62	..	6.2	41.5

WEDNESDAY

Breakfast

      30 grams of 10 per cent fruits
      1 egg—scrambled
      50 grams of 32 per cent cream
      25 grams of bacon (fat)
      30 grams of butter

Dinner

      75 grams of 3 per cent vegetables
      50 grams of 32 per cent cream
      45 grams of meat (fresh)
      50 grams of butter

Supper

      75 grams of 3 per cent vegetables
      30 grams of 10 per cent fruits
      50 grams of 32 per cent cream
      25 grams of bacon (fat)
      26 grams of butter

FOOD VALUE

Carbohydrate :15   Protein :25.1   Fat :182

Food	Grams						
	Morning	Noon	Evening	Total	Carbohydrates	Protein	Fat
Vegetables, 3 per cent	..	75	75	150	4.5	1.5	....
Fruit, 10 per cent ...	30	..	30	60	6.	.6	....
Eggs	1	..	..	1	..	6.	6.
Cream, 32 per cent ..	50	50	50	150	4.5	3.	48.
Bacon (fat)	25	..	25	50	..	5.	33.5
Meat (fresh)	..	45	..	45	..	9.	4.5
Butter	30	50	26	106	..	..	90.

THURSDAY

Breakfast

      25 grams of 10 per cent fruits
      50 grams of 32 per cent cream
      34 grams of bacon (fat)

Dinner

      50 grams of 32 per cent cream
      42 grams of butter
      50 grams of salmon
         tomato soup (Recipe 2)

Supper

      50 grams of 3 per cent vegetables
      25 grams of 10 per cent fruits
      50 grams of 32 per cent cream
      70 grams of butter
         deviled eggs (Recipe 3)

FOOD VALUE

Carbohydrate :15   Protein :25   Fat :182

Food	Grams						
	Morning	Noon	Evening	Total	Carbohydrates	Protein	Fat
Vegetables, 3 per cent	..	..	50	50	1.5	.5	...
Fruit, 10 per cent...	25	..	25	50	5.	.5	...
Cream, 32 per cent..	50	50	50	150	4.5	3.	48.
Bacon (fat)	34	..	..	34	..	3.	22.5
Butter	..	42	70	112	..	..	95.
Salmon	..	50	..	...	..	11.	6.5
Deviled eggs.......	..	..	R3	...	1.	6.	10.
Tomato soup	..	R2	..	...	3.	1.	...

FRIDAY

Breakfast
>   30 grams of 10 per cent fruits
>   1 egg—scrambled
>   50 grams of 32 per cent cream
>   20 grams of butter
>   24 grams of bacon (fat)

Dinner
>   75 grams of 3 per cent vegetables
>   50 grams of 32 per cent cream
>   70 grams of butter
>   50 grams of halibut

Supper
>   75 grams of 3 per cent vegetables
>   30 grams of 10 per cent fruits
>   50 grams of 32 per cent cream
>   19 grams of butter
>   25 grams of bacon (fat)

FOOD VALUE

Carbohydrate :15   Protein :25   Fat :182

Food	Grams						
	Morning	Noon	Evening	Total	Carbohydrates	Protein	Fat
Vegetables, 3 per cent	..	75	75	150	4.5	1.5	...
Fruit, 10 per cent...	30	..	30	60	6.	.6	...
Eggs	1	..	..	1	..	6.	6.
Cream, 32 per cent..	50	50	50	150	4.5	3.	48.
Butter	20	70	19	109	..	..	92.5
Bacon (fat)	24	..	25	49	..	4.9	33.
Halibut	..	50	..	50	..	9.	2.5

SATURDAY

Breakfast

    30 grams of 10 per cent fruits
    1 egg, scrambled
    50 grams of 32 per cent cream
    21 grams of butter
    14 grams of bacon (fat)

Dinner

    75 grams of 3 per cent vegetables
    50 grams of 32 per cent cream
    60 grams of butter
    50 grams of roast beef

Supper

    75 grams of 3 per cent vegetables
    30 grams of 10 per cent fruits
    50 grams of 32 per cent cream
    30 grams of butter
    15 grams of bacon (fat)

Food Value

Carbohydrate :15   Protein :25   Fat :182

Food	Grams						
	Morn-ing	Noon	Eve-ning	Total	Carbo-hydrates	Protein	Fat
Vegetables, 3 per cent	..	75	75	150	4.5	1.5	...
Fruit, 10 per cent...	30	..	30	60	6.	.6	...
Eggs	1	..	..	1	..	6.	6.
Cream, 32 per cent..	50	50	50	150	4.5	3.	48.
Butter	21	60	30	111	..	..	94.
Bacon (fat)	14	..	15	29	..	2.9	19.5
Roast beef	..	50	..	50	..	11.	14.5

Baked Egg with Cheese (Recipe 1)[3]

Egg	1
Cream	15 grams
Pale American cheese	25 grams
Butter	5 grams

Butter a small dish with 5 grams of butter. Add the egg, 15 grams of cream, and 25 grams of cheese grated fine. Bake in moderate oven until cheese is melted. Food value, 1 gram carbohydrate, 14 grams protein, and 22 grams fat.

Tomato Soup (Recipe 2)[3]

Clear broth	1 cupful
Tomatoes, cooked	80 grams
Onions, uncooked	10 grams

To one cup of clear broth add 80 grams of tomatoes and 10 grams of onions cut fine. Cook for fifteen minutes. Season with salt and pepper and serve. Food value, 3 grams carbohydrate and 1 gram protein.

Deviled Egg (Recipe 3)

Egg, hard cooked	1
Lemon juice	5 grams
Mustard	a few grains
Paprika	a few grains
Salt and pepper	a few grains
Melted butter	5 grams
Salad dressing with mineral oil	1 teaspoonful

Cut egg in halves (lengthwise). Mix yolk thoroughly with seasonings, melted butter, and salad dressing. Refill white. Food value, 1 gram carbohydrate, 6 grams protein, and 10 grams fat.

Thrice Boiled Bran

Boil bran for fifteen minutes in a large amount of water, at least 8 cups of water to 1 cup of bran. Pour bran into a sieve, let cold water run through it for several minutes, then drain. Repeat three times, then dry bran carefully.

Bran Cakes [3]

Bran, thrice boiled	3 cupfuls
India gum	1 tablespoonful
Baking Powder	5 grams
Salt	¼ teaspoonful
Eggs	2
Egg yolks	2
Butter	50 grams
Water	180 grams

Mix ingredients in order given and bake in a moderate oven. This recipe makes twelve cakes. Food value of three cakes, 4 grams protein and 17 grams fat.

[3] From Wilder, *Primer for Diabetic Patients*, W. B. Saunders Co., Philadelphia.

Chicken Supreme [4]

Chicken, weighed cooked	50 grams
Egg	½
Milk	50 grams
Celery	25 grams
Salt and pepper	a few grains
Butter	5 grams

Beat egg slightly, add chicken and celery, cut in small pieces, milk, salt and pepper. Put in buttered mold, set in pan of hot water and bake in moderate oven until firm. Food value, 3 grams carbohydrate, 17 grams protein, and 17 grams fat.

Wilted Lettuce with Egg Yolk [4]

Lettuce	30 grams
Bacon	30 grams
Egg yolk	1
Vinegar	1 tablespoonful
Salt and pepper	a few grains

Cut bacon into small pieces and fry until crisp, add egg yolk, and scramble. Then add vinegar and pour mixture over lettuce. Food value, 1 gram carbohydrate, 5 grams protein and 26 grams fat.

Scalloped Cabbage with Bacon

Cabbage, weighed uncooked	50 grams
Bacon	30 grams
Bran, thrice boiled	1 tablespoonful

Boil cabbage (cut fine) in a large amount of water for twenty minutes, drain, and put into a small casserole or cup. Cut bacon into small pieces, fry until crisp, then add one tablespoonful of dry, thrice boiled bran. Add this mixture to cabbage and bake in hot oven ten minutes. Food value, 2 grams carbohydrate, 4 grams protein, and 20 grams fat.

Pancakes

Cellu flour	¼ cup
India gum	¼ teaspoonful
Starch free from baking powder....	⅓ teaspoonful
Salt	⅛ teaspoonful
Saccharin	¼ grain
Hot water sufficient to moisten	
Egg	1

Mix the dry ingredients and add warm water enough to make a stiff batter. Fold this mixture into the well-beaten egg. Fry on a hot griddle greased with mineral oil or the fat that is allowed in the diet. Makes 4 cakes.

Note: To be satisfactory the pancake batter must be more moist than for ordinary pancakes. Food value (due to one egg—average size), protein 6 grams, Fat 6 grams.

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[4] *Ibid.*

Ice Cream [5]

Cream, 40 per cent..............	100 grams
Egg	1
Water	½ tablespoonful
Saccharin	½ grain
Vanilla	⅓ teaspoonful

Beat the yolk of egg very light. Add cream slowly. Fold in beaten white of egg. Then add vanilla and saccharin which has been dissolved in ½ tablespoonful of water. Freeze. Food value, carbohydrate 3 grams, protein 8 grams, fat 46 grams.

Chocolate Ice Cream

Cream, 40 per cent	100 grams
Egg yolk	1
Cocoa	5 grams
Water	¼ cupful
Saccharin	½ grain

Beat yolk of egg until very light and add one-half the cream. Mix cocoa and water together and boil for three minutes. Add the remainder of the cream and reheat. Allow this mixture to cool and then add to egg yolk and cream mixture to which has been added the saccharin. A few drops of vanilla may be added if desired. Freeze. Food value, carbohydrate 5 grams, protein 5 grams, fat 47.5 grams.

Stewed Prunes

Dried prunes (as purchased)............	35 grams
Water	140 grams

Soak prunes over night in water. Cook slowly for twenty minutes. Liquor in which prunes have been cooked must be included in the serving. Food value, carbohydrate 21.5 grams, protein 0.5 gram, fat 0.

Cellu-Bran Wafers

Cellu-flour	25 grams
Dry bran, thrice boiled	60 grams
Cinnamon	1 teaspoonful
India gum	10 grams
Mineral oil	3 tablespoonfuls
Hot water	100 grams
Saccharin	1 grain
Vanilla	½ teaspoonful
Salt	a few grains

Mix dry ingredients thoroughly. Add oil, vanilla, and hot water, in which saccharin has been dissolved. Spread very thin on an oiled baking sheet, cut into squares, and bake in a slow oven until dry. No food value.

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[5] *Ibid.*

Mayonnaise

Salad oil, ¾ cupful	155 grams
Egg yolk	1
Vinegar	1 tablespoonful
Salt	1 teaspoonful
Pepper	a few grains

Beat the egg yolk until thick. Add oil drop by drop, beating all the time. Then add a little vinegar, then oil slowly, then vinegar as necessary. Add salt and pepper. Have ingredients cold. Food value, protein 2 grams, fat 161 grams.

D'Zerta

D'Zerta [6]	1 envelope
Boiling water	½ cupful

Dissolve the contents of one envelope in half a measuring cupful of boiling water. Stir well and set away to cool. Food value, protein 2 grams.

D'Zerta Bavarian

Raspberry D'Zerta	1 envelope
Cream, 40 per cent	50 grams
Boiling water	½ cupful

Dissolve the contents of one envelope of D'Zerta in ½ cupful of boiling water. When D'Zerta begins to thicken, add cream and beat until D'Zerta and cream are thoroughly mixed. Put into mold and chill. Food value, carbohydrate 1.5 grams, protein 3 grams, fat 20 grams.

Cocoa

Cocoa	5 grams
Cream, 40 per cent	50 grams
Water	100 grams
Saccharin	½ grain

Mix cocoa and water together and bring slowly to the boiling point. Add the cream and reheat. The saccharin may be added after the cocoa is removed from the flame. Food value, carbohydrate 3.5 grams, protein 2 grams, fat 21.5 grams.

Saccharin may be used freely for sweetening. It is not usually necessary to use more than 1½ grains a day. The saccharin should be added to the preparation after it has cooled. Canned fruits, packed or canned without sugar, usually contain about 50 per cent of the carbohydrate content listed. The protein content may be considered unchanged.

After the patient has been put on a proper prescription, that is, a diet which will maintain the desired weight and keep the convulsions under control, this diet is continued for from three to six months. At the end of this period, the carbohydrate is increased 5 grams each month, for six months, provided the patient continues free of seizures. At the end

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[6] D'Zerta is carbohydrate-free jello.

of six months, or from nine to twelve months after the diet is instituted, the protein is increased 10 grams. Thereafter, the protein increase of 10 grams is alternated each month with a 5-gram increase of carbohydrate. At the end of fifteen months or two years, the fat may be decreased by 10 grams each month to keep the desired weight and satisfy the appetite. It is advisable to supply cod-liver oil once daily to all patients on this diet. It is also advisable to include liver twice a week.

For the preparation of the diet lists and sample diets the author is indebted to Miss Alice Cattonach, dietitian of the New Haven Hospital.

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NOTE: Therapeutic agents appear in black-face type, as **Bismuth**. Subjects other than treatment appear in plain capitals, as ACIDOSIS. All headings are alphabetized and the relation of the subheadings represented by dashes.

(1)

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